Volume XXI

Number 4

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DISEASES OF THE NERVOUS SYSTEM

A Practical Journal on Psychiatry and Neurology

APRIL
1960

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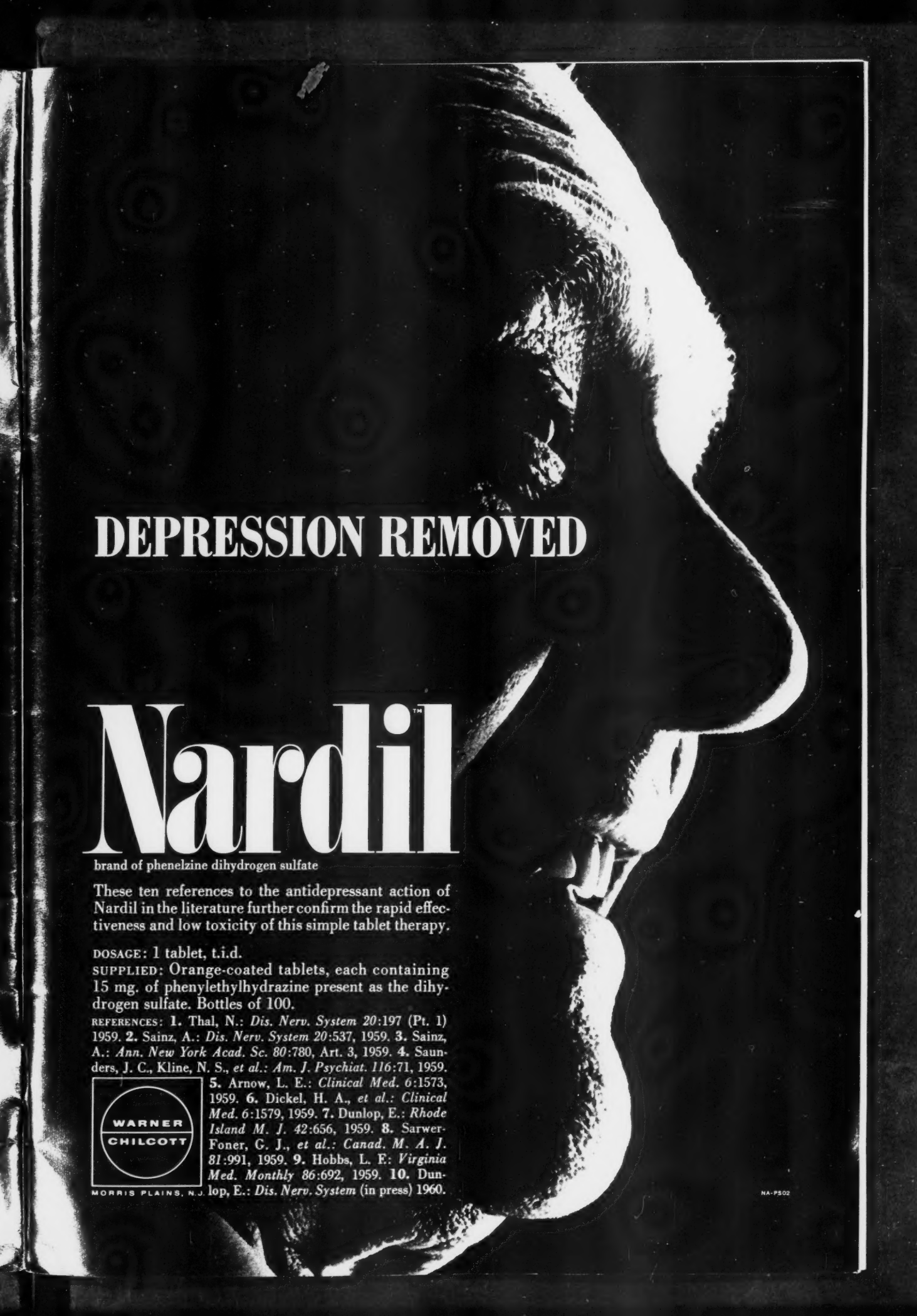

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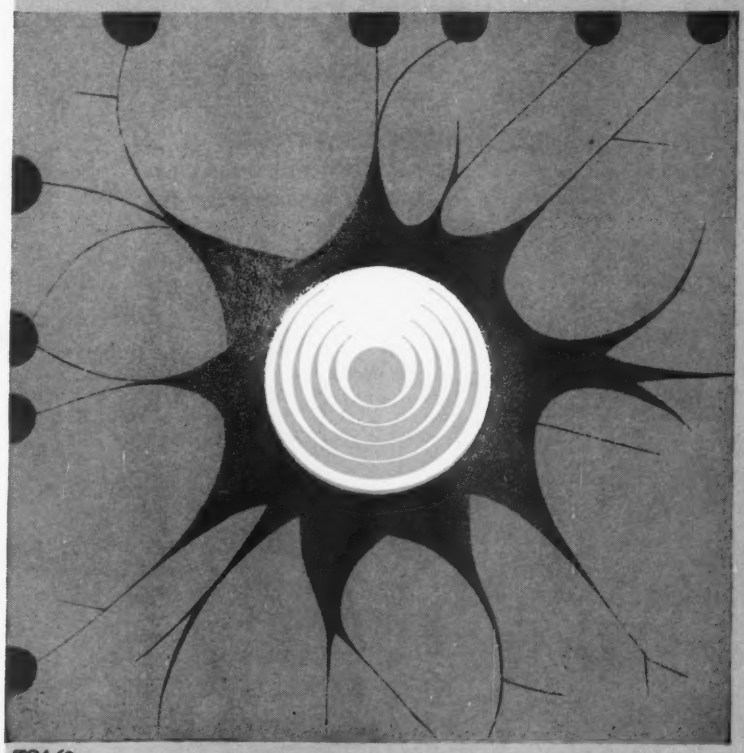

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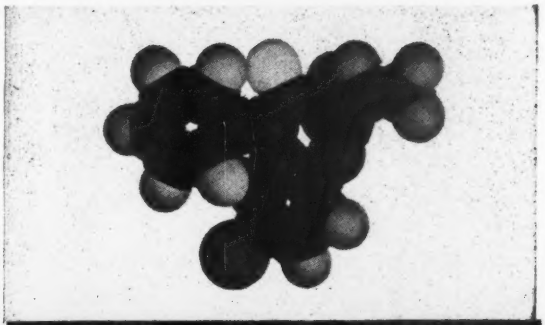

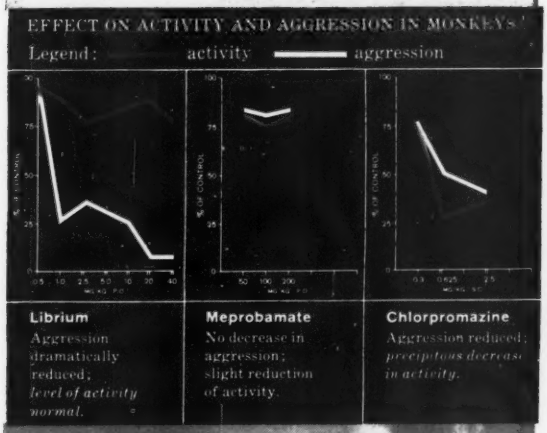
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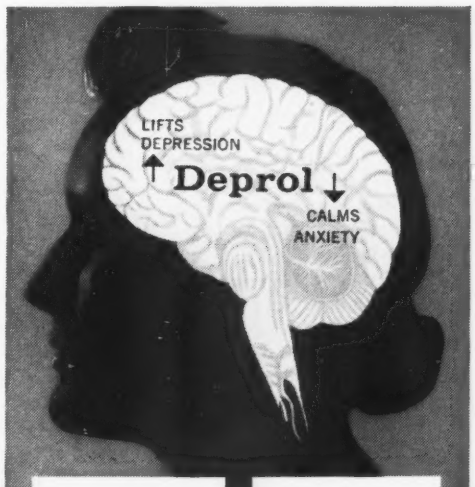

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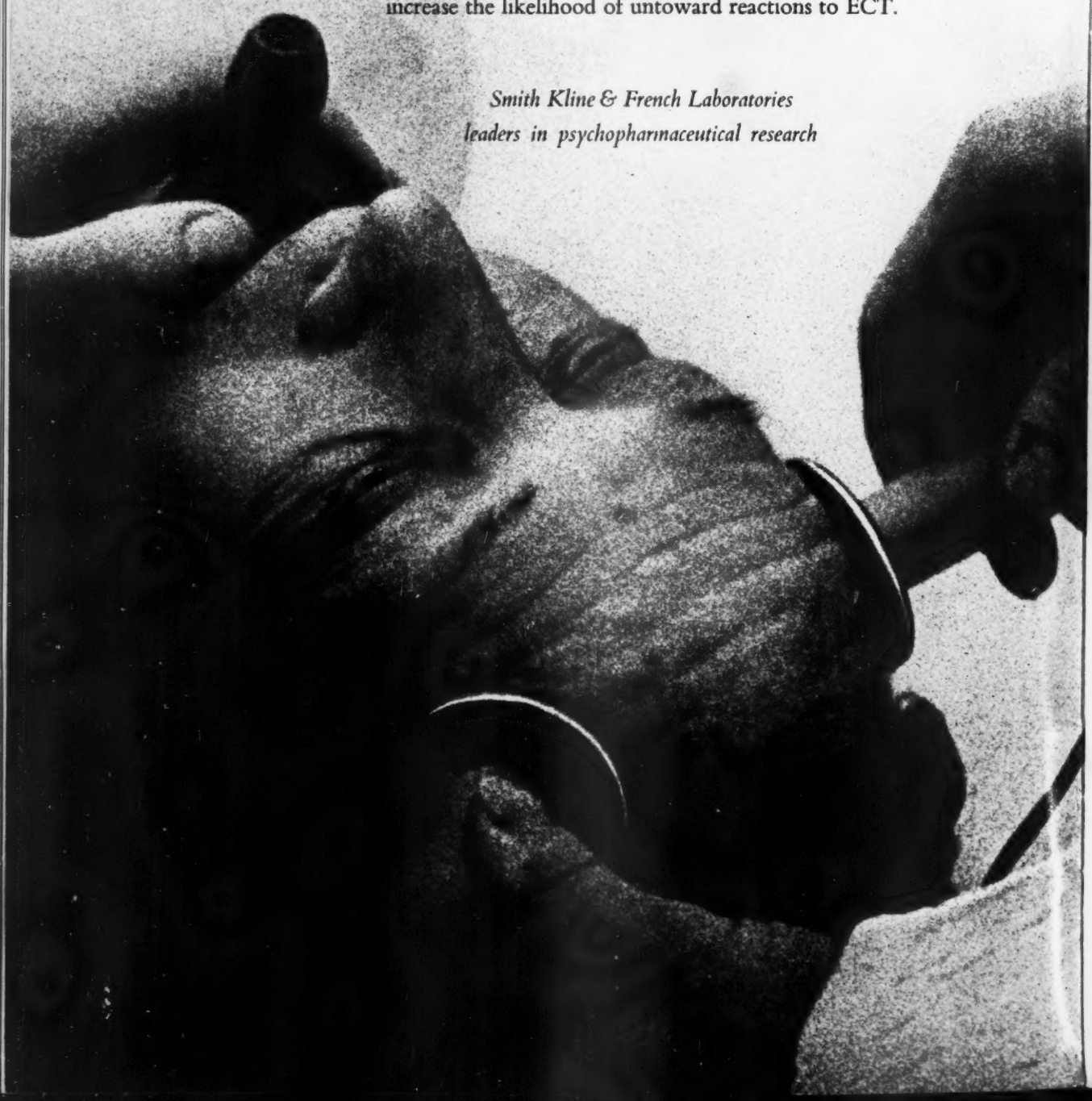

Volume XXI APRIL 1960 Number 4

DISEASES *of the* Nervous System

A PRACTICAL JOURNAL ON PSYCHIATRY AND NEUROLOGY

Glucose Tolerance and Insulin Sensitivity

MARGARET R. READ, M.D.

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A number of studies on carbohydrate tolerance and insulin sensitivity in patients given insulin coma therapy for various psychoses have been done. However, these studies do not agree in their methods or their conclusions and in some the series are quite small. The investigators have often been impressed by an apparent metabolic or hormonal disturbance and some postulate this as a cause of the psychoses; others identify this as a concomitant finding. Harris, Blalock and Horwitz,[1,2] in 1938 studied 17 psychotics, nine both before and after insulin coma therapy. They reported a decrease in carbohydrate tolerance after treatment in six of their nine cases. One showed an increased tolerance. Banting, Franks, and Gairns[3] found that insulin coma therapy increased the insulin resistance of an insulin-resistant patient. Kaplan and Low[4] in 1939 found a delay in return to fasting levels both in glucose tolerance test and insulin tolerance test done on a group of schizophrenics, but could find no correlation between insulin tolerance test and coma dose of insulin.

Altschule[5,6] has noted impaired glucose tolerance, insulin resistance, increased tendency toward glycogen formation and relatively high 17 ketosteroid output in schizophrenic psychoses. After electrocoma therapy or insulin coma therapy, he found the glucose tolerance is often improved, especially if the test is made several weeks after the last treatment. He found no correlation of change in glucose tolerance with response to electroshock therapy.[7]

Looney and Cameron[8] found a definite decrease in the glucose tolerance in eight of their nine cases tested shortly after the conclusion of insulin coma treatment of schizophrenia.

In 1940 Lundbaek and Magnussen,[9] in Copenhagen, did extensive and well controlled studies on 20 patients with schizophrenia or schizophreniform psychoses and paid particular attention to carbohydrate content of the diet. Contrary to the expectation following Himsworth's[10] conclusion, "the greater the amount of carbohydrate in the diet the greater the sensitivity of the organism to insulin." They could not lower the insulin coma dose on a high carbohydrate diet. They used two diets, one 50 gm. carbohydrate plus 50 to 150 gm. saccharase for the interruption of coma; the other 500 gm. carbohydrate plus the 50 to 150 gm. of saccharase used for interruption of coma. They found that glucose tolerance test curves were higher on a low carbohydrate diet. On the insulin tolerance test, the patients on the high carbohydrate diet showed a more abrupt fall in blood sugar and the curves were lower. After juggling the diets and carefully controlling their experiment they concluded that the minimal coma dose is not dependent upon the amount of carbohydrate supplied, nor can it be expected that insulin coma therapy can be carried on a lower dose of insulin by restricting patients to a special diet. They postulate that differences in coma dose may be due to difference in total glycogen deposit in the organism and more particularly, differences in the small glycogen deposits in the brain itself.

Meduna, Gerty, and Urse[11] in 1942 studied the anti-insulin effect of the blood of cases of schizophrenia. They found that serum from schizophrenic patients injected into rabbits decreased the effect of insulin in the rabbit's blood sugar levels. They also found a delay in return of blood sugar level to normal after intravenous glucose infusion in 20 schizophrenics. They concluded that there was a disturbance in carbohydrate

This study was done at the Cleveland Psychiatric Institute, Cleveland, Ohio.

metabolism characterized by delayed utilization of blood sugar, due (1) to a low insulin level or slow mobilization of insulin, or (2) an overactivity of some product, hindering the effect of insulin. They covered this by postulating an anti-insulin factor. They also suggested a sub-division of schizophrenia into two pathogenically different forms based on insulin sensitivity blood sugar curves.

Harris[12] did studies on the anti-insulin factor of the serum on rabbits but got variable results. He found no correlation between insulin sensitivity tests and insulin coma dose in fourteen patients. Three of his patients showed increased insulin sensitivity after insulin coma therapy. This was not necessarily accompanied by a change in clinical condition. He thought that the factors antagonistic to the lowering of blood sugar by insulin differ, at least in part, from those which bring about recovery from the hypoglycemic state.

Goldner and Ricketts[13] could find no insulin inhibition by the serum of schizophrenic patients when the serum was injected into rabbits. They felt that insulin resistance was limited to its rare occurrence in diabetes or may develop as a direct result of insulin treatment.

In 1943, Freeman, Looney, Hoskins and Dyer[14] compared 32 schizophrenics and 20 normals using insulin sensitivity and epinephrine effects on the blood sugar levels. They found that the responses of blood sugar in schizophrenics to insulin and epinephrine moved in a narrower range than the normal. They divided their schizophrenic patients into two groups according to insulin responsivity but this does not parallel variations in psychiatric status. Their results agreed with those of Meduna, Gerty and Urse[11] but not with Gellhorn, Feldman and Allen[15] who postulated a predominance of vagoinsulin influence in schizophrenics. Freeman, et al.[14] suggested a greater reactivity in the sympathico-adrenal sphere in their patients since the hypoglycemic effects of insulin were antagonized. They concluded that insulin resistance and the enormous doses of insulin required to produce coma offer a lead for further investigation into carbohydrate metabolism of the central nervous system in cases of schizophrenia.

Braceland, Meduna, and Vaichulis[16] in 1945 studied the delayed action of insulin in schizophrenia and reconfirmed their belief in an antiinsular factor. The 29 schizophrenics showed a 35% loss of fasting blood sugar after insulin. Of 247 schizophrenics, 29% were hypoglycemic and the highest fasting blood sugar levels were at the upper limits of normal. The Exton Rose two-dose one-hour glucose tolerance test showed that of 102 schizophrenics, 37 had normal curves, 16 flat, or descending curves, and 49 had an abnormal rise during the second half-hour.

In 1949, Borenz, Schuster, and Downey[17] studied the effect of insulin coma therapy on glucose metabolism of 16 young male schizophrenics. They did intravenous glucose tolerance tests, insulin sensitivity tests, and epinephrine tests before and after insulin coma therapy and found no consistent change in test results. The average figures suggest some increased tolerance to insulin and epinephrine, indicating a possible increased rigidity of homeostasis. They found no correlation between insulin tolerance test and subsequent dose of insulin necessary to induce coma. They felt that schizophrenics do not differ from normals.

Thorley and Kay[18] in 1951 studied the biochemical aspects of hypoglycemic coma in 35 male patients, not all of whom were schizophrenic, some showed schizoid or paranoid features. The potassium and phosphate and glucose showed the most uniform changes, the former two changes agreeing with levels usually found when glucose is removed from the blood. They suggested that the adynamogenesis produced by large doses of insulin underlies the therapeutic effect of insulin coma therapy and inhibits those organs such as adrenals, that are normally responsible for counteracting insulin.

In 1952 Freudenberg[19] made observations on the relation between insulin coma dosage and prognosis in 68 males and 78 female schizophrenics and 31 atypicals. He found a greater number of good responses among females than males, and the males generally required higher doses. This suggested that sex steroids may be a factor. He found lower insulin coma doses have a tendency to be correlated with good therapeutic response. Female schizophrenics of less than six

months duration needed lower dose than males with illness of same duration. This difference disappears with longer duration of illness. Atypical cases, that is, those with pseudoneurotic or manic depressive features, had lowest minimal coma dose of insulin and the best therapeutic response. Body index type was not significantly correlated with prognosis and neither was the weight.

Meduna and Vaichulis[20] reported the presence of a hyperglycemic factor in urine of so-called schizophrenic patients. Meduna and McCulloch[21] have reclassified these schizophrenics as "oneirophrenics" and have claimed that a correlation exists between the presence of a hyperglycemia factor in the urine and an abnormal carbohydrate metabolism as demonstrated by a resistance to insulin, a pseudo-diabetic reaction to the Exton-Rose test and a protracted sugar-tolerance curve during an intravenous glucose-tolerance test. Morgan and Pilgrim[22] confirmed the presence of a hyperglycemic factor in the urine of some schizophrenics and indicate the factor to be a protein or a material bound to it. A comparable factor in normal male urine was not found.

These various studies on glucose metabolism in schizophrenia show many contradictions and inconsistencies, but do offer a hint that some derangement of normal physiology and biochemistry does exist in the schizophrenic process.

Method

Thirty-five patients between the ages of 19 and 42 with diagnoses of schizophrenic reactions of various types were selected for this study because the psychiatric staff had considered them good candidates for insulin coma therapy.

There were 17 females and 18 males and the duration of illness was from a few months to 4½ years, but all were thought to be in an acute phase of their illness. The patients were on a high carbohydrate diet adequate in protein and fat and all had been eating well. The tests were performed after a 12-hour fast and the patients were lying comfortably in bed with one or two attendants present at all times. Prior to testing, the patients had been fully informed as to what was to happen and had already entered into group activities with the other patients on insulin therapy. The morale of the group was excellent and the majority were most cooperative. It is felt that fluctuating anxiety played little part in affecting the test results. On the first day a 5.0 c.c. sample of venous blood was drawn for glucose determination and the patients were given ⅓ gram of glucose per kg. of body weight, as 50% solution of glucose in water, intravenously. One-half hour later another 5.0 c.c. of venous blood was drawn for glucose determination and a second dose of glucose amounting to ⅓ gram per kg. of body weight as 50% solution of glucose in water was given intravenously. Further blood glucose determinations were made at 1 hour, 1½ hours, 2 hours, 2½ hours, and 3 hours after the initial intravenous dose of glucose.

On the second day the insulin sensitivity test was done as follows: At zero hour, the fasting blood sugar was drawn and 0.1 unit of crystalline insulin per kilogram of body weight was injected intravenously. Blood was drawn for glucose determination every ½ hour for 2 hours. The blood sugar determinations were done by the Folin-Wu method modified for the Klett-Summerson colorimeter. It was felt that it was not necessary to determine true blood sugar because Borenz, Schuster and Downey[17] checked non-glucose reducing substances in schizophrenic patients and found close agreement with Somogyi's[23] original statement that the non-glucose reducing substance was quite uniform. They found that the non-glucose reducing substance in the blood of schizophrenics varied 18-27 mg. per cent and averaged 23 mg. per cent. The factor remained fairly constant regardless of the variations of the blood sugar following intravenous injection of glucose and of insulin.

The patients were then placed on insulin coma therapy and the minimum coma dose determined. Therapy consisted of a total of from 24 to 51 hours of coma, each coma lasting up to one hour. Treatment was given five days a week. Coma was defined as that state in which the patient no longer responded to sight, sound or pain with a purposeful movement. Minimal coma dose was the smallest dose of regular insulin which

could be counted on to produce coma in the patient on consecutive days.

Four to eighteen days after cessation of treatment the glucose tolerance test and insulin sensitivity test were repeated in the above manner on 20 of the patients.

Results

Of the 35 patients tested in this series 29 of them or 83% showed abnormal glucose tolerance curves when tested with the two dose one hour Exton-Rose glucose tolerance test given intravenously (Table I). The criteria of abnormality with this test are 1) a fasting blood glucose level above 130 mg. per 100 c.c., 2) a half-hour blood glucose level above 170 mg. per 100 c.c., 3) a one hour blood glucose more than 10 mg. per 100 c.c. higher than the half-hour level.[24] In normal individuals the blood sugar does not rise above 170 mg. per 100 c.c. and returns to normal fasting levels within two hours. The second dose of glucose one-half hour after the first does not prevent this fall in blood sugar in normal individuals tested a half-hour later. All but three of this series of patients had normal fasting blood sugars and these ranged from 131 to 134 mg. per 100 c.c. The half-hour blood sugar levels ranged up to 322 mg. per 100 c.c. and the one hour blood sugar levels ranged up to 293 mg. per 100 c.c. At the end of two hours all but three patients were back to their normal fasting blood sugar.

Normal insulin sensitivity is described as

TABLE I

Glucose Tolerance Levels

Pre-Insulin

Patient	Fasting Blood Sugar	½ hour	1 hour	1½ hours	2 hours	2½ hours	3 hours
AB	119	165	210	142	117	111	117
CB	134	166	196	118	108	113	107
FB	115	144	172	109	94	106	113
RD	92	123	150	102	71	66	84
SD	122	182	226	137	100	107	102
VD	104	210	163	133	99	85	88
WD	113	165	131	103	90	77	88
FE	88	154	176	98	61	85	85
AG	124	162	119	104	95	92	105
HG	106	200	270	195	138	99	87
AH	99	113	140	95	89	75	77
BH	115	194	262	172	106	104	116
DH	92	151	173	129	88	77	84
RI	107	164	211	139	98	97	86
AK	96	201	156	127	127	91	86
NK	95	179	135	100	95	83	86
BL	93	184	227	169	113	79	68
OL	93	122	132	352	89	372	84
TL	113	169	129	117	63	77	127
WL	108	191	207	114	79	80	80
AM	117	170	250	142	112	124	108
BM	109	234	293	214	145	116	96
DM	104	183	148	117	108	95	102
FM	134	171	144	116	129	124	127
GM	90	124	86	78	81	85	85
MN	99	143	192	125	102	85	76
DN	125	225	174	134	108	94	100
GP	97	125	137	112	387	80	73
ER	88	129	145	84	68	75	79
OS	104	153	198	152	108	86	76
RS	111	152	172	106	71	102	96
AS	110	322	182	130	42	97	87
AT	92	153	117	99	89	86	91
DW	131	227	240	97	59	80	87
AZ	113	202	290	212	162	113	103

TABLE II

Insulin Sensitivity

Pre-Insulin

Patient	Fasting Blood Sugar	½ hour	1 hour	1½ hours	2 hours
AB	112	55	71	105	105
CB	114	55	83	100	104
FB	109	60	76	97	107
RD	92	39	45	62	72
SD	102	69	90	100	113
VD	97	46	64	87	97
WD	103	38	73	84	98
FE	95	55	68	72	83
AG	99	54	81	104	104
HG	99	47	80	85	90
AH	116	50	74	83	107
BH	104	66	57	87	86
DH	94	40	65	87	96
RI	97	48	59	60	65
AK	101	87	68	73	80
NK	100	67	58	81	90
BL	99	47	66	78	84
OL	102	37	62	95	90
TL	97	50	80	96	95
WL	112	45	57	74	87
AM	117	77	84	92	108
BM	101	39	76	97	107
DM	99	52	70	83	93
FM	115	57	79	91	112
GM	91	34	46	56	65
MN	94	42	70	52	91
DN	118	53	73	89	84
GP	97	34	62	95	90
ER	96	40	60	98	98
OS	115	62	84	95	118
RS	106	36	63	84	106
AS	97	53	78	82	84
AT	95	44	82	93	95
AZ	112	54	69	90	98

a greater than 50% drop in the blood glucose level from the fasting level within one-half hour after the administration of 0.1 unit of crystalline insulin per kilogram of body weight. Insulin resistance is less than 50% drop in glucose level from the fasting level one-half hour after intravenous insulin in the above amounts. Twenty of the patients or 57% showed a greater than 50% drop in the glucose level one-half hour after the administration of insulin and were therefore insulin sensitive (Table II); 28 patients showed a delay beyond 1½ hours in returning to normal fasting glucose levels. In normal persons return to fasting levels are expected to occur 75 minutes after the administration of insulin.

The disturbance in carbohydrate metabolism gives no clues as to the optimal coma dose of insulin for insulin coma therapy. Insulin sensitivity and insulin resistance bear no relationship to initial or optimal coma dose of insulin. Neither of these tests give any indication as to response of the patient to insulin coma therapy (Table V).

Previous insulin administration has been shown to cause a temporary loss of tolerance for carbohydrate in normal men.[25-28] Joslin and Marble recommend that no glucose tolerance test for diagnosis should be carried out unless the subject has received no insulin for three days. In this series four to 18 days elapsed after cessation of insulin treatment before the glucose tolerance and insulin sensitivity tests were repeated.

In the 20 patients tested after insulin coma therapy, eighteen, or 90%, showed an abnormal glucose tolerance (Table III). One person who had shown an abnormal curve now had a normal curve and three who had been normal were now abnormal. Seven of the twenty patients, or 35%, showed insulin resistance. However, seven of the patients had changed from resistance to sensitivity, or vice versa, after insulin coma therapy (Table IV). Nine were insulin sensitive and remained so after insulin coma therapy.

These findings show no correlation with improvement following insulin coma therapy and insulin coma therapy does not significantly alter the glucose tolerance or insulin sensitivity.

Discussion

The present studies confirm that there is considerable derangement in the carbohydrate metabolism in the schizophrenic process. Most of these patients had received elec-

TABLE III

Glucose Tolerance Levels

Post-Insulin

Patient	Fasting Blood Sugar	½ hour	1 hour	1½ hours	2 hours	2½ hours	3 hours
RD	109	196	152	126	122	122	126
VD	99	198	162	129	99	78	73
WD	102	199	156	118	90	90	82
AG	88	145	107	87	82	77	88
DH	86	179	241	180	132	111	35
RI	97	181	167	136	103	83	71
AK	155	302	264	182	156	137	115
BL	126	185	207	111	107	96	99
OL	109	187	236	199	118	94	87
WL	92	186	174	93	52	45	63
BM	112	221	291	190	147	107	80
DM	95	192	155	117	100	75	75
FM	98	167	100	98	106	95	116
GM	126	253	169	142	139	128	126
DN	97	204	150	117	88	85	79
GP	114	489	251	156	104	95	77
ER	131	225	241	141	107	105	101
RS	102	181	201	129	93	77	88
AT	112	194	110	99	106	96	100
DW	128	237	265	149	96	84	89

TABLE IV

Insulin Sensitivity

Post-Insulin

Patient	Fasting Blood Sugar	½ hour	1 hour	1½ hours	2 hours
RD	113	44	53	83	98
VD	102	55	67	70	82
WD	114	42	66	73	94
AG	89	33	45	58	80
DA	86	87	147	73	78
RI	92	44	62	73	91
AK	132	94	69	81	85
BL	123	42	46	66	86
OL	126	39	49	73	105
WL	96	41	50	60	66
BM	136	51	64	87	102
DM	100	67	61	73	83
FM	101	24	60	72	87
GM	115	44	62	118	89
DN	96	50	55	75	79
GP	111	42	57	79	77
ER	124	63	77	96	117
RS	106	45	42	66	91
AT	107	56	59	72	98
DW	130	43	48	64	96

trocoma therapy without improvement. We do not know what effect ECT has on the blood-brain barrier. The electrocoma therapy should have removed most of the patients fitting Meduna's[29] classification of oneirophrenia. Typically, oneirophrenics show insulin resistance, disturbed carbohydrate tolerance with an up and up response on the Extron-Rose test; show a primary illusionary psychosis or confusional state and respond readily to electrocoma therapy. In the present group, prior electrosoma therapy probably explains the smaller number of insulin-resistant patients. Even after electrocoma therapy 23 or 63% of our patients were still abnormal on the Exton-Rose test and showed the up and up response.

TABLE V

Patient	Sex	Age	Initial Coma Dose of Insulin	Usual Coma Dose of Insulin	Maximal Coma Dose	Diagnosis—Type of Schizophren.	Improved	Hours of Coma
			units	units	units			
AB	M	27	400	50	400	Paranoid	Yes	24
CB	F	25	400	223	400	Paranoid	Yes	30
FB	M	25	700	200	700	Paranoid	Yes	31
RD	M	26	500	210	500	Paranoid	No	42
SD	F	36	360	170	360	Paranoid	No	36
VD	F	19	300	150	400	Catatonic	Yes	47
WD	M	32	500	210	500	Paranoid	No	49
FE	F	28	400	200	400	Undiff'ted	Yes	50
AG	M	20	400	240	400	Paranoid	Yes	37
HG	F	19	300	120	300	Catatonic	No	35
AH	M	42	600	200	600	Paranoid	No	47
BH	F	29	200	60	200	Affective	Yes	48
DH	F	32	400	130	400	Paranoid	No	45
RI	M	26	450	190	450	Catatonic	Yes	46
AK	F	33	300	220	300	Paranoid	No	39
NK	M	30	600	180	600	Paranoid	No	26
BL	M	26	600	250	600	Paranoid	Yes	42
OL	F	25	400	250	400	Catatonic	Yes	47
TL	M	27	400	250	400	Catatonic	No	43
WL	F	24	400	150	400	Catatonic	No	51
AM	F	25	450	150	450	Paranoid	No	50
BM	M	35	400	230	400	Catatonic	Yes	50
DM	M	31	600	200	600	Undiff'ted	No	33
FM	M	20	500	210	500	Paranoid	No	49
GM	F	23	300	160	300	Paranoid	Yes	45
MN	F	31	400	250	400	Paranoid	Yes	33
DN	F	27	400	190	400	Paranoid	No	36
GP	F	33	400	180	400	Catatonic	Yes	50
ER	M	25	500	210	500	Paranoid	No	49
OS	M	26	350	150	350	Undiff'ted	Yes	50
RS	M	27	400	200	400	Paranoid	Yes	50
AS	M	24	500	290	700	Undiff'ted	Yes	51
AT	F	33	400	130	400	Paranoid	Yes	19
DW	F	24	700	140	700	Paranoid	Yes	50
AZ	M	28	500	190	500	Paranoid	No	42

Whatever defect in the carbohydrate metabolism was demonstrable by our tests, it remained unaltered by insulin coma therapy. McCulloch[30] suggested that some part of the brain serves as a gland of internal secretion, to produce some unknown hyperglycemic factor. It is unknown how the central nervous system knows the level of sugar in the blood or the full story of how it controls that level. Gellhorn[15] thought that excited insane patients have too much insulin in their circulation and that their blood sugar is roughly normal only because their own insulin fails to affect them.

It is becoming more and more apparent that the diagnosis "schizophrenia" is a broad and poorly defined term which includes a variety of mental disturbances. As further studies in metabolism, biochemistry and the responses to physical and chemical therapies are carried out, we may hope to have a clearer understanding of these mental illnesses and better differential diagnoses.

These psychoses are not primarily environmentally-induced ideational disturbances, but actual disturbances in physiological processes due to unknown factors—metabolic, hormonal, biochemical. The need for further investigation is apparent. We need to know more about the effects of insulin on the brain. We need to know why most of the patients can no longer handle carbohydrate after insulin coma therapy and why some patients change their insulin-sensitivity and what has happened to the blood-brain barrier in electrocoma and insulin coma therapy.

Summary

1. Thirty-five schizophrenic patients between the ages of 19 and 42, with short duration of illness, most of whom had failed to respond to electrocoma therapy were tested with the two-dose intravenous Exton-Rose glucose tolerance test and insulin-sensitivity test.

2. Eighty-three percent of the patients showed abnormal carbohydrate tolerance and 43% showed insulin resistance.

3. None of these patients were diabetic.

4. No direct correlation between the re-

sults of these tests and the coma dose of insulin or response to insulin coma therapy was found.

5. Repetition of the tests after insulin coma therapy in twenty of the patients showed that a few patients changed their resistance to insulin and a few changed their carbohydrate tolerance. Ninety per cent showed an abnormal glucose tolerance and 35% showed insulin resistance.

6. The present studies indicate that we need to know more about the effects of insulin on the brain. We need to understand why some patients, after insulin coma therapy, can no longer handle carbohydrate and why some show a change in insulin resistance. We need to know what has happened to the blood-brain barrier during insulin coma therapy.

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Paraplegia of Sudden Onset Due to a Cirsoid Angioma (Arteriovenous Aneurysm) of the Spinal Cord

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The diagnosis of the cause of rapidly developing paraplegia can at times be extremely difficult. A review of the literature assigns numerous causes, including thrombosis,[1-6] infection,[7-9] tumors,[10-22] and vascular anomalies.[23-37] The final diagnosis,[38-40] however, is often established by inference rather than by direct observation at operation or autopsy. Unfortunately the number of spinal cord autopsies continues to be extremely small (1 to 2%) as compared to brain autopsies.[23,41-44] The following case illustrates diagnostic problems and the value of postmortem examination.

W.M., age 56, white male, was admitted to the hospital on December 3, 1947. His chief complaint was severe pain in the left side radiating to the left shoulder. The history revealed that the patient was well until two days before admission. After the evening meal he had gone to the basement to do some "tinkering." This was not heavy work. He had been in the basement for approximately 1½ hours when he had a sudden severe pain in the right upper quadrant of the abdomen. The pain "shot" upward to the right shoulder and then down into the middle of his back. He fell to the floor and "thought that he was going to die." The pain lasted less than a minute but left him short of breath and paralyzed from the ribs downward. A note made by his family physician revealed that when first observed, his color was ashen as he lay motionless on the floor. He was covered with profuse perspiration and complained of severe chest pain. The pulse was feeble and the heart sounds were distant and somewhat irregular. At the time of the first examination paralysis was not complete in both lower extremities. There was loss of feeling below the umbilicus. The knee and ankle reflexes were absent.

On arrival at the hospital one hour after the onset of his illness, he was immediately placed in an oxygen tent. He was now completely paralyzed in the lower extremities. There was a loss of bowel and bladder control. Urinary retention developed.

The possibility of rupture of the anterior spinal artery was considered by the family physician.

Past History: He had the usual childhood diseases with no known sequellae. He had typhoid fever at age 12. There was no history of operations or injuries.

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Family History: His mother died of heart trouble at age 50. Father died of a stroke at 63. There were no known familial diseases.

Physical Examination: Blood pressure 120/70, pulse 88, respiration 24, temperature 98.6°. He was a well developed, well nourished, white male lying in bed unable to move his lower extremities. His hair was sparse and gray. The sclerae were clear and the conjunctivae were normal in color. The pupils were equal and regular and reacted to light and accommodation. The fundae were normal except for slight A. V. nicking. The ears and nose were negative. He was completely edentulous. The tongue was moist and the tonsils were atrophied. The neck was supple. There were no enlarged cervical nodes. The thyroid was enlarged to the left. Cardiac rhythm was regular. The lungs were clear bilaterally. Breathing was diaphragmatic in type. The abdomen was markedly distended. There was no tenderness and no rigidity. The liver and spleen were not palpable. The rectal and bladder sphincters were in spasm.

The clinical impression was that this patient had had a coronary thrombosis and/or a dissecting aortic aneurysm.

Course in the Hospital: Urine on admission was straw colored, acid, contained 30 mg. albumin, 150 to 200 white blood cells per high power field. Blood examination revealed 15.2 grams of hemoglobin, 5,180 white cells, 75% polys, 28% lymphocytes. The blood serology was negative.

Neurologic Examination on the second hospital day revealed a complete flaccid paralysis in the lower extremities. The superficial and deep reflexes were abolished. Mass reflexes could be demonstrated on plantar stimulation. The pain sense was abolished on the left side to a level of T-6 and on the right side to T-8. Tactile sensation was intact everywhere. Pallesthesia was intact. Joint sensation was intact everywhere. Pallesthesia was intact. Joint sense was abolished in the lower extremities. A lumbar puncture one week after admission revealed grossly bloody fluid. The pressure was 155 mm. of water. There was no evidence of a block on bilateral jugular compression. It was the impression that the patient had a hemorrhage of the anterior spinal artery.

Munro tidal drainage of the bladder was instituted. X-rays of the lower cervical and upper thoracic spine revealed no abnormalities. The cranial nerves were intact. The deep reflexes were equal and active bilaterally in the upper extremities. Motor function and sensation was intact in the upper extremities. A lumbar puncture performed two weeks after admission was clear with a pressure of 150 mm. of water. Three weeks after admission the

patient was able to move the right great toe. Pain and temperature were perceived to T-12. Ten weeks after admission he was able to move the right foot and flex the right knee slightly. He had developed a large decubitus over the sacrum which required plastic surgery. The wound broke down. A culture revealed hemolytic staphylococcus albus and nonhemolitic streptococci. Streptomycin sulfa-mylon was instilled into this cavity. Smear and culture became negative. A fluctuant mass developed in the left gluteal region toward the trochanter which required drainage. Smear and culture were negative.

The patient's general condition was fair. He was then a problem in fluid balance, plus a bladder infection and paraplegia. Mass reflexes developed almost from the beginning of his illness. There was a dissociation between tactile sense and joint sense in the lower extremities. This was studied from the standpoint of blood supply,[42,43] of the spinal cord and location of the fibers in the posterior funiculi which carry joint sense and touch. His course was gradually downhill and he expired 7½ months after admission.

Autopsy: Gross examination of the spinal cord showed evidence of an old hematomyelia and extensive myelomalacia, at the level of the 8th thoracic segment. In addition there was chronic pyelonephritis, chronic cystitis, sacral decubiti, lobar pneumonia, central lobular necrosis of the liver and chronic cholangitis. There was also moderate cortical depletion of the adrenals, arterial and arteriolar nephrosclerosis, infection of the spleen and kidneys, benign prostatic hypertrophy and a Meckel's diverticulum. Gross appearance and microscopic examination of the brain revealed no abnormalities. The entire spinal cord was removed. The anterior spinal artery and vein appeared to be intact except for an area of atrophy from T-4 through T-8 segments. Fifteen blocks were made, ten above and four below the lesion. Because of the value of this case for instruction, and its planned use in teaching, the whole cord was sectioned. Every tenth section was stained (Niemer's stain, Morgan's stain, Van Giesen's stain). Several stains were used on the lesion (Lillie's H. & E. stain, Gomori's Trichrome stain, and Masson's Trichrome stain).

At T-8 (the lesion) Fig. 1, the architecture of the cord was entirely lost. In the anterior half of the cord there was a large lumen of the artery which was filled with antemortem laminated clot. The elastic tissue was hypertrophied. In close proximity to the artery there were two veins which showed

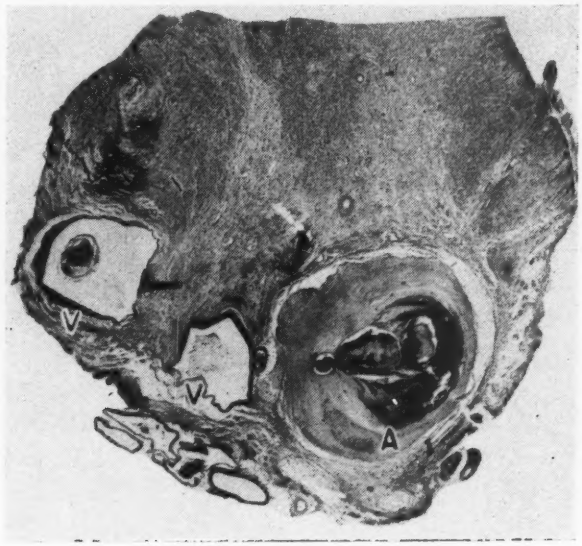

Figure 1. The lesion—T-8 segment.

A—Anterior spinal artery with thrombus formation.
V—Veins.

The lesion extended from T-4 through T-8 segments. At T-8 in the anterior half of the cord, the artery lumen is filled with an antemortem laminated clot.

The elastic tissue is hypertrophied.

The veins show thickening of the elastic tissue.

The normal architecture of the cord is lost. Numerous large pigmented phagocytes are present throughout cord substance.

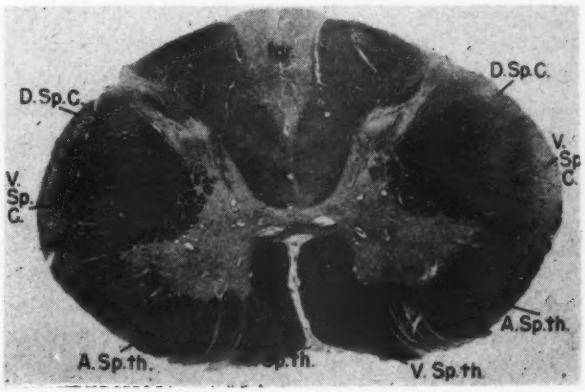

Figure 2. C-4 Segment (Oral to lesion).

fgr.—fasciculus gracilis
D Sp. C—Dorsal spinocerebellar tract
V Sp. C—Ventral spinocerebellar tract
V Sp. th—Ventral spinothalamic tract
A Sp. th—Anterior spinothalamic tract

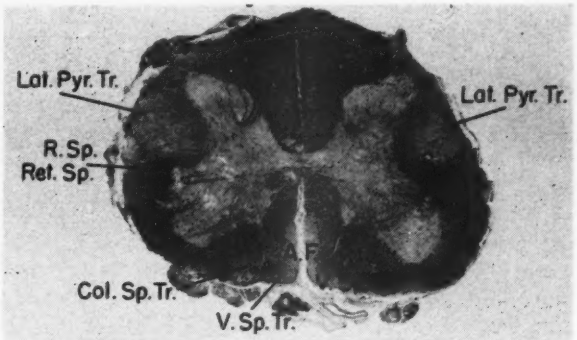

Figure 3. L-3 segment (caudal to the lesion).

Lat. pyr. Tr—Lateral pyramidal tract
V. Sp. Tr.—Vestibulo-spinal tract
R. Sp.—Rubro spinal tract
Ret. Sp.—Reticulo spinal tract
Col. Sp.—Colliculospinal tract
A.F.—Anterior funiculus: medial longitudinal fasciculus, tectospinal and vestibulospinal tracts.

The vestibulo spinal tract, reticulospinal and vestibulospinal tract are indicated by varying degrees of demyelinization in anterior and lateral columns.

thickening of the elastic tissue. Within the surrounding cord substance there were large pigmented phagocytes. The fibre tracts could not be recognized on any section at the site of the lesion. The posterior arteries were intact. The diagnosis of cirsoid angioma was established.

A section at segment C-4 (oral to the lesion, figure 2) shows demyelinization of the posterior medial columns (fasciculus gracilis). There is also degeneration of the dorsal spinocerebellar tracts and to a lesser degree the ventral spinocerebellar tracts. The anterior and ventral spinothalamic tracts likewise show degeneration.

A section at L-3 segment (caudal to the lesion, Fig. 3) reveals degeneration of the pyramidal tracts, vestibulospinal, reticulospinal, rubrospinal, colliculospinal, and the anterior funiculus.

Summary

A case of paraplegia of sudden onset due to a cirsoid angioma (arteriovenous aneurysm) of the spinal cord with autopsy is presented. The diagnosis was not established until after serial sections of the lesion were made and studied with special stains.

Ascending and descending degeneration of some of the long tracts of the spinal cord are present because the interval between onset of the illness and time of death was seven and one half months.

Serial sections of the cord showing degeneration of these tracts are being used for teaching at the University of Cincinnati College of Medicine.

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A Study of Head-Banging in Infants and Children

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JOHN B. MURPHY, M.D., and RAYMOND E. LESSER, M.D.

Introduction

Head-banging is defined as a rhythmic motor habit characterized by repeated striking of the head against a solid object; it is probably the most spectacular motor rhythm seen in infants and children, yet, little detailed information is available in the pediatric, neurologic, and psychiatric literature on the phenomenon. One of the reasons for this is that it is difficult to study infants and children with this disorder. Although the parents and frequently the neighbors, are acutely aware of the child's head-banging, very few physicians have actually witnessed the acts. The sight of a child rocking back and forth on all fours and pounding his skull against the headboard of a bed, 60 to 80 times a minute is certainly most alarming to the parents. Parents consult the physician because they fear the child will injure himself. or are concerned because the loud monotonous noise disturbs the household during sleeping hours. Also there is the fear that the behavior of the child indicates a serious neurological or psychiatric disorder. However, in many cases of head-banging the parents do not seek medical help.

We have studied 135 cases of head-banging which were encountered in our private practice of pediatrics, in terms of the natural history of the phenomenon. Because of the lack of detailed information on this subject, it was felt that such a study was a necessary first step before an understanding of the disorder could be obtained and a rational method of treatment developed. After presenting our findings, we will attempt to integrate them within the framework of current neurologic, psychologic and psychiatric theories of head-banging and of motor rhythms in general.

Review of the Literature

Several theories have been advanced to explain the phenomenon of head-banging and associated motor rhythms. In an excellent discussion of the role of all rhythmic pattern in childhood, Lourie[1] in 1949, emphasized that these activities may be seen as a normal phenomenon satisfying instinctual need and facilitating motor and personality development. He states, "that rhythmic activities seem to serve the secondary function of the expression of pleasure, release of tension, or to give compensatory satisfaction." He reasons that the secondary values may cause the persistence of these patterns past the infantile period. Although his study was based on 120 children in a pediatric clinic, Lourie did not break down the number of head-bangers, body-rockers, or head-rollers in his series. He presented no detailed information on the head-bangers as a group except to note the importance of auditory stimuli in these cases.

Spitz[2] makes no reference to head-banging in describing a series of 87 body-rockers in an institution. He found the highest incidence of body-rockers to be between six and eight months. Only 12 cases occurred before six months. He felt that a disturbed relationship existed between the infant and the mother and that rocking was a symptom of the lack of emotional interchange between the mother and child. He felt that body-rocking is a pleasurable and narcissistic activity and a solace to the child. It is surprising to note that Spitz uncovered no head-bangers in his study.

In another study of motor rhythms Mittelman[3] felt that motor rhythms in general are the consequence of inherent rhythmic drives or motor urges. It is interesting to note that in a study of motor rhythms in animals, including monkeys and apes, Harlow[4] noted rhythmic rocking movements but specifically noted no head-banging activities in any of his animals.

Richmond[5] in a study of one head-banger noted the onset of body-rocking on hands and knees sometime after 4½ months of age. Head-banging and body-rocking continued in

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the all fours position until ten months, when the patient began rocking in a sitting position and began head-banging occipitally. Richmond noted an early interest in, and fondness for music and rhythms in this stage. He, also, observed that the child, after one year, head-banged as an attention getting device. He, also, noted a delay in the onset of speech. He concluded that there is no one specific etiological factor in head-banging but that a multiplicity of factors may be involved.

Anna Freud[6] mentioned head-banging occurring in six cases of children in an institution. She attributed head-banging to self-directed aggression towards the child's own body and felt it was affected by institutional life.

Teplitz and Bromberg[7] in a psychodynamic study of head-banging in 12 children and their parents, stressed the auditory and strong tactile stimulation in head-banging which they feel is a distinguishing characteristic of head-banging as opposed to body-rocking. They feel that head-banging is a purposeful response to internal or external sources of tension, in that it brings the tension under the control of the infant's own body and musculature. Interest in human response is given up during the period of head-banging, since the external inanimate object does not itself react, initiate emotional response, or otherwise participate in the activity. They mentioned teething as an internal source of tension which may be associated with head-banging.

Fitzherbert[8] in a study of one case, advanced the theory that headbanging represents the infant's attempt to re-experience the mother's heart beat when it is held in her arms. She presented no experimental data to support this theory, however.

Ilg and Ames[9] list a series of personality traits which they, on the basis of their clinical experience, feel are characteristic of head-bangers. These authors feel that head-bangers frequently show unusual interest in sounds and music and sing on pitch at an early age. (This is also our experience.) They may be ritualistic and compulsively neat. Although they have considerable energy, they are slow to approach a strange person or a new activity and slow to give it up. They may have temper tantrums and are considered to be poor sleepers.

Material and Method

One hundred and thirty-five cases of head-banging were found by routinely questioning mothers, in private pediatric practice. In the cases studied by the authors and those contributed by other pediatricians, data on growth and development were obtained by examining the office records. A good number of additional cases were uncovered by asking the mother if she knew of head-banging infants or children among her friend's children. All cases reported to be head-bangers had the diagnosis confirmed by checking with the patient's physician. All of the cases studied came from white middle and low-income families. Infants with outstanding orthopedic, visual, and auditory abnormalities or those suspected of gross mental retardation or neurologic diseases were excluded from the study.

Psychometric studies were done in twelve of the cases studied by one of the authors, and are being reported in another paper.[7]

Head-banging is a relatively infrequently encountered problem. Without the co-operation of other pediatricians the number of cases compiled in this study could never have been accomplished.

Electroencephalographic studies were done on seven of our cases, by Gibbs and Gibbs. At our request they reviewed the electroencephalograms of 21 cases referred to their laboratory with a diagnosis of head-banging. The data on all these cases is included in the present study.

Results

No studies are available regarding the incidence of head-banging in infants and children. The incidence of head-banging in the senior author's private practice of pediatrics was calculated to be 3.6% with 1168 infants and children studied. De Lissavoy[13] calculated head-banging in a group of 825 children to be 6.5%. In the total sample of 135 cases, males predominated over females 105 to 30, a ratio approximately 3.5 to 1, an obviously significant difference. This 3.5 to 1 ratio was also noted in the senior author's cases.

Head-banging begins at a mean age of eight months, with a standard deviation of 2.5 months, indicating that the vast majority of cases begin head-banging between the ages of 5 and 11 months (see Figure 1). There were only nine cases that began head-banging after the age of 12 months.

Head-banging occurred most frequently, in 78% of the cases, at bed time, usually at night, but also during daytime naps. Approximately 50% of the children in our sample engaged in this activity for less than 15 minutes at a time. While there is considerable variability in this facet of the problem, 26% of the group are reported to head-bang for one hour or longer at a time. When one considers that these children have been observed by us to head-bang between 60 to 70 bangs per minute, the total number of head-bangs each night is extremely large. Although head-banging usually occurs in children who are awake, 35% of the children in the sample were also observed to head-bang while asleep. Of this group, over half also head-bang while awake.

In keeping with the findings that most head-banging occurs in connection with bed-time activities, 100 cases in our sample were found to bang against the head-board of the bed (see Figure 2). One-third of the children in our sample show multiple head-banging, that is, they bang against the head-board and the side of the bed, on the wall near the bed, and the back of chairs. It was found that 86% of the cases head-bang on all fours in the mid-frontal region. The next most common group were those who banged in the sitting position, 18% of the cases being occipital bangers exclusively.

Figure 3 illustrates the presence of associated motor rhythms in children who head-bang. It is clear that the large majority of the group, 67%, also indulge in body rocking. A clinical note at this point: body-rocking often precedes the onset of head-banging and may continue after the head-banging has ceased. Obviously, in these cases of frontal banging, in which the children are on all fours, the body rocking movement is an integral part of the head-banging activity. Figure 3 shows that 27% of the children show combined associated motor rhythms, and that approximately 18% are

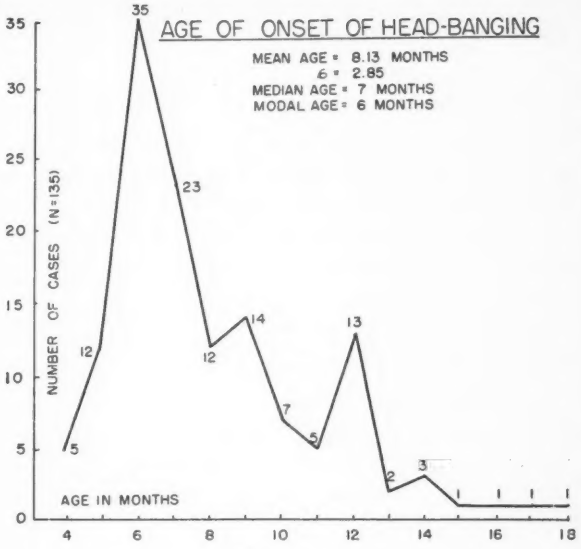

Figure 1.

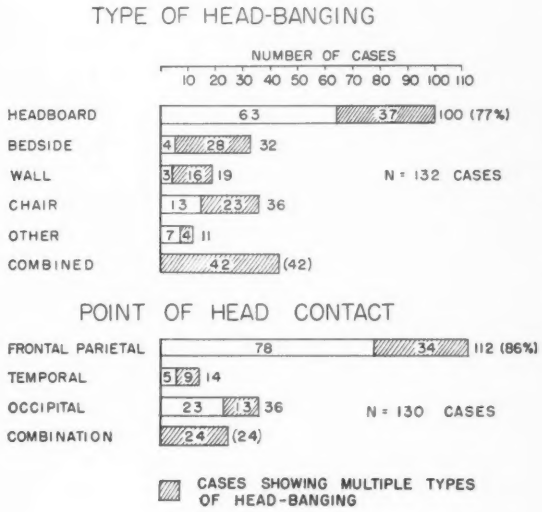
TYPE OF HEAD-BANGING
NUMBER OF CASES
10 20 30 40 50 60 70 80 90 100 110
HEADBOARD 63 37 100 (77%)
BEDSIDE 4 28 32
WALL 3 16 19
CHAIR 13 23 36
OTHER 7 4 11
COMBINED 42 (42)
N = 132 CASES
POINT OF HEAD CONTACT
FRONTAL PARIETAL 78 34 112 (86%)
TEMPORAL 5 9 14
OCCIPITAL 23 13 36
COMBINATION 24 (24)
N = 130 CASES
CASES SHOWING MULTIPLE TYPES OF HEAD-BANGING

Figure 2.

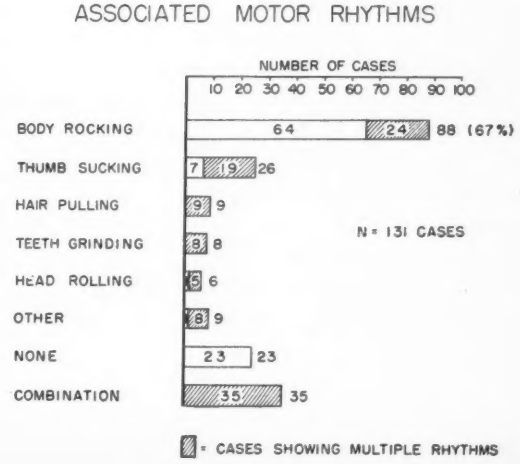
ASSOCIATED MOTOR RHYTHMS
NUMBER OF CASES
10 20 30 40 50 60 70 80 90 100
BODY ROCKING 64 24 88 (67%)
THUMB SUCKING 7 19 26
HAIR PULLING 9 9
TEETH GRINDING 8 8
HEAD ROLLING 5 6
OTHER 8 9
NONE 23 23
COMBINATION 35 35
N = 131 CASES
= CASES SHOWING MULTIPLE RHYTHMS

Figure 3.

reported to show no motor rhythms other than the head-banging. It is important to note that only 9% of our cases were thumb-suckers. According to Traisman[14] 45.6% of normal healthy infants seen in a pediatric practice were reported to be thumb-suckers

In evaluating the relationship of head-banging with other behavior, 91% of the cases show no crying associated with head-banging (see Figure 4), 68% showed no temper tantrums; 66% of the children showed no night crying in combination with teething. It is important to note that the average age of eruption of the central and lateral incisors was 7.5 months and 9.85 months respectively, a range in which the onset of head-banging occurs. In several cases, head-banging would stop and again start with the eruption of a new group of teeth.

In evaluating family factors related to head-banging, the following facts were found: 1) Head-banging occurred in other children of the family in only 20% of the cases. 2) Head-banging occurs somewhat more frequently in families with two children, but may be said to be almost evenly distributed among families containing either one, two, or three children. 3) Head-banging occurs in the first child of the family in 53% of the cases, and in the second child in the family in 32% of the cases. 4) Separation of mother and child by virtue of hospitalization of either, or by divorce or separation, or mother working occurred in only 27% of the cases, indicating that by and large, the head-banging children are not significantly separated from their mothers.

Although the evaluation of the mother-child relationship by the pediatrician represents only a gross approximation of this relationship, 68% of the cases were felt to show a good mother-child relationship, 15% were felt to have fair mother-child relationship and 17% were felt to have a poor mother-child relationship.

In our series, head-banging disappeared in 54% of the cases, with a mean chronologic age of 47.4 months at the time of our contact with them. Among these children it was found that the duration of the phenomenon averaged 17 months, continuing to a mean chronologic age of 24.8 months (see Figure 5). Less than 20% of this group continued head-banging for longer than 18 months.

Of the other 46% of our cases, head-banging persisted up to the end of the present study. In this group the mean duration of the head-banging was 27.3 months, and the children were a mean chronologic age of 34.6 months at the time of our contact with them. Analysis of the data on this group showed that among children still banging, there were actually two distinct sub-groups. The first consisted of 32 children with a mean chronologic age of 17.6 months at the time of contact who had begun to head-bang at a mean chronologic age of 7.9 months, and who had continued for a mean duration of 10.1 months. Thus, this is a group of children who have not completed the course of the symptom, so to speak, and could prob-

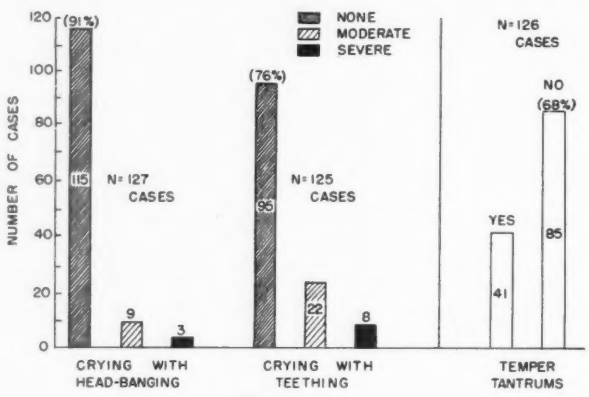

Figure 4.

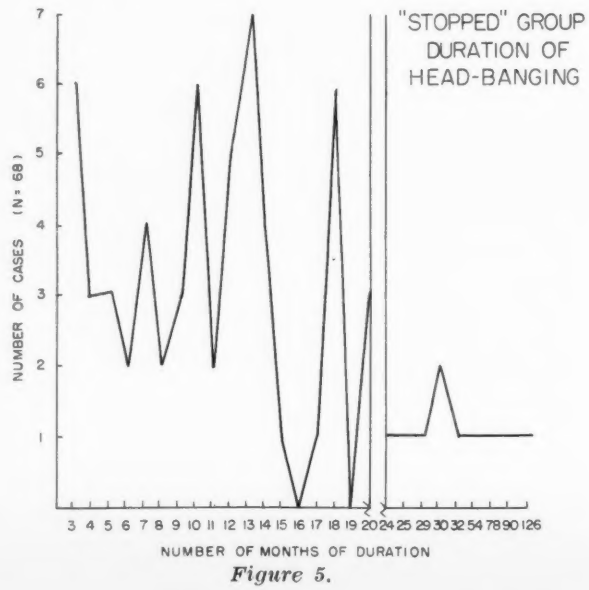

Figure 5.

ably be regarded as a "normal" group in comparison with the group in which head-banging had already stopped.

The second sub-group consisted of 25 children with a mean chronologic age of 56.4 months who began head-banging at a mean chronologic age of 8.16 months and who continued to head-bang for a mean duration of 48.3 months. This latter group, coupled with those 13 children who are no longer head-bangers, but who continued for more than 18 months, constitute the chronic or persistent cases. Thus, approximately 30% of the infants and children in our sample are or have been chronic head-bangers. Unlike the first group, in which head-banging lasts for a period of about 18 months, children in this latter group may continue head-banging for as long as 10½ years. However, inspection of our data on our chronic head-bangers shows no fundamental distinguishing characteristics which would set them apart from the other group.

In regard to the question of the EEG finding in cases of head-banging, Gibbs and Gibbs[12] have uncovered 21 cases of head-bangers referred specifically for EEG because of persistent head-banging. All cases have been reported as normal. In reviewing our own data, we have found an additional seven cases which also were described as having normal EEG. The absence of abnormal electroencephalograms in these cases suggests that head-banging is not an epileptic or epileptiform disorder and is not related to an acute or progressive cortical disorder. Also, it should be stated that we have not had one case of severe or permanent intracranial injury in 135 cases reported in this study. However, abrasions and contusions about the mid-frontal and occipital region have been noted. On the other hand, no evidence of acquired injury to the brain has been noted clinically or on EEG.

Discussion

Perhaps the outstanding feature which all the theories of head-banging advanced in the literature have in common, is the absence of clear cut experimental evidence to support them. The uniformity of onset of this phenomenon at age 8 months in all sub-groups in our population could be taken as support for the theory that head-banging reflects a maturational pattern emerging as an inherent function of the organism in the transitional phase from sitting to crawling. The fact that the age of onset also tends to correspond to the period of eruption of central and lateral incisors may indicate the role that tension reduction may play in the development of head-banging behavior. Because of the early age of onset, it is unlikely that attention seeking as a primary factor in head-banging can be argued, but in the chronic cases this secondary value may be significant. The absence of crying associated with head-banging and the apparent absence of pain raises a question about the acceptability of the idea that this act is a form of self-inflicted aggression against the body. However, it may be argued that the absence of overt response to pain during head-banging does not rule out the fact that pain may be present, but neutralized by kinesthetic, auditory, rhythmic pleasures.

These children tend to show various motor rhythms in combination with head-banging. Thus, they may be a group which is hypersensitive to tactile, kinesthetic and auditory stimulation, responding to these stimuli through the modality of body rhythms rather than, say verbal activities. Although no electroencephalographic abnormalities have been found in head-bangers it seems likely that hyperactivity of some type, possibly in deep centers, gives rise to this phenomenon. A normal electroencephalogram is found in children with choreoathetosis, with Sydenham's chorea and in patients with Parkinsonism. The electrical activity of at least two-thirds of the brain is not recorded in the electroencephalogram. Furthermore, there are types of neuronal function which are not electrogenic or which, at least, produce nothing that can be recorded in the electroencephalogram. The behavior pattern of these head-bangers indicates that they constitute a group in which some inherent central nervous rhythmicity is more strongly expressed than in the majority of infants of their age.

Treatment

Head-banging in infancy is a benign disorder which requires no medical treatment

beyond reassurance of the mother that the child will outgrow the symptom and that no injury to the brain will result. In the severe chronic cases of head-banging persisting beyond the age of three years, it is our opinion that a neurologic and psychiatric evaluation is needed. We have employed various sedatives and tranquilizing drugs in a series of severe chronic head-bangers and have been impressed with the benefit obtained in some cases. It is our opinion that drug therapy is indicated in selected cases of persistent head-banging.

Conclusion

The average head-banger usually is a male child who begins head-banging at about 8 months of age, continuing for about 17 months until he is 25 months of age. He is usually awake and in bed at the time of head-banging, usually banging against the headboard while rocking on all fours and hitting his head in the mid-frontal area. The average head-banger does not cry in association with his headbanging, he generally shows no evidence of temper tantrums. Crying in connection with teething is rare. He is most often also a body-rocker which often preceded the head-banging. He does very little thumb-sucking. His central and lateral incisors tend to erupt at a period which marks the onset of the head-banging phenomenon. Head-banging is more frequent in the first child in the family. He has not been significantly separated from his mother. His relationship with the mother is generally regarded as adequate.

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Patient and Staff Reactions to a Change in Procedure on a Psychiatric Ward

MATTHEW DUMONT, B.A., ROBERT S. DANIELS, M.D., PHILIP M. MARGOLIS, M.D., ROBERT C. CARSON, PH.D., and JOHN HAM, M.S.W.

The rapidly increasing interest in the psychiatric ward as a therapeutic community is reflected in the contributions of Jones,[1] Stanton and Schwartz,[2] Caudill[3] and Parker.[4] These authors have focused attention on decision-making, communication, staff morale and the interrelations of ward procedures. The purpose of this paper is to describe some of these transactions in the context of a specific sequence of events on a psychiatric unit. The sequence consisted of combining an open and a closed section into a single closed ward, and, 18 days later, restoring the previous division. Subsequent reactions to this abrupt change in procedure illustrate the differing effects on patients and staff of an alteration in administrative policy.

The inpatient psychiatric service of the University of Chicago Clinics is specifically adapted to diagnosis and short term intensive treatment. It is a 19 bed unit customarily divided into an open and a closed section by a locked steel door. Patients are admitted to one of the 11 beds in the closed section. At the recommendation of his therapist, the patient is moved to one of the eight beds on the open section, which communicates with the rest of the hospital through an unlocked glass door. The ward is staffed with two psychiatrists, a psychologist, two social workers, two residents, a medical and a psychology intern, a recreational and an occupational therapist, one senior and six junior medical students, nine nurses, three attendants, four orderlies, and a ward clerk. The primary function of the service is teaching, and the teaching orientation is basically psychoanalytic.

The temporary consolidation of the open and closed sections into a single closed ward was made in order to expedite new closed section admissions. At the time, the closed section was filled to capacity while the open section housed only two patients.

From University of Chicago Clinics, 950 E. 59th Street, Chicago 37, Illinois.

Methods of Data Collection

In the evaluation of the effects of the two changes in administrative policy, the following sources of material were used:

1. Nurses' notes.
2. Sleep and sedation records.
3. Unstructured interviews with patients by a social worker who was not a member of the inpatient staff.
4. Written opinions of the ward change by staff members.
5. Observations of patient group therapy meetings, staff conferences, and nurses' daily reports.
6. General observations by the entire research team.

Patient Response to Unifying of Ward

Open Section Patients:

Patients were informed by their individual therapists of the impending alteration in procedure two or three days before it took place. At the time of the first change, the two patients on the open section were Miss Wise and Mrs. Gilson. Another patient, Mrs. Rust, was enjoying open section privileges in anticipation of moving there. On the night following the change, Mrs. Gilson required sedation (after having slept well without it for some time), and Miss Wise slept five hours instead of her usual eight. Nurses' notes show that Miss Wise was "More depressed"; Mrs. Gilson was "Quite tremulous," and Mrs. Rust was "More tense, annoyed at the new system." On one occasion Miss Wise said, "I don't like those patients being out here." She added angrily, "If I don't get out of here I'm going to have a relapse." At another time Mrs. Gilson said, "If you take any of my privileges away I'm going to sign out."

Although initial statements in group therapy about the opening of the inner door were approving, further discussion revealed that Mrs. Gilson, Miss Wise, and Mrs. Rust resented the change, and felt a loss of differen-

tiation from "disturbed" patients. At subsequent meetings these patients continued to desire some differentiation from what they continued to call "closed ward" patients. Two days later they vigorously objected to paying for staff lunches at picnics, although no objection had been raised to this policy in the past.

Closed Section Patients:

There was nothing remarkable in the sleep and sedation records of the patients on the closed section. Nurses' notes indicated that six had good or average days and three had relatively poor days. These three expressed indifference to the change, one telling the interviewing social worker that he "didn't give a damn about the door or anything." The others on the closed section uniformly approved the increased freedom and comfort of the open door.

Patient Response to Redivision of the Ward

When the ward was redivided, Mrs. Gilson, still on the open section and soon to be discharged, heartily approved. She said that the open section offered a milestone in a patient's progress, and that it gave the better patients greater independence of staff, making them feel less inadequate and childlike. Although Mrs. Rust, now on the open section, was pleased to be "free" of the more disturbed patients whom she claimed had been annoying her, she experienced a moderate return of her compulsive handwashing.

The three other patients now on the open section were there for the first time. Although when on the closed section they had approved of opening the door, two of them were now glad it was locked. Mrs. Wallace said that the closed door helped her to draw the distinction between herself and sicker patients, and that the other patients' troubles were with their "minds," while hers were with her "feelings." Mrs. White said that some of the patients needed the locked section for their own protection, but that not enough discrimination was used in making the decision. At the time of the interview Mrs. Rale had just been moved after having spent several days on the closed section. She remained critical of the locked door. She said that the few days behind the door had "hit her very hard." She had felt at the time that she was losing ground and that her troubles were pushing in on her. She saw no sense to the change back.

Closed Section Patients:

Records for the night following the change back to the divided ward showed a peak of sedation orders for closed section patients. These patients denounced the locked door as restricting their freedom or denying them certain physical conveniences. A new patient, a paranoid woman who slept poorly that night, wrote: "The doors are being closed because of me." Another patient felt that "something ominous" was happening in relation to the door, but she was unable to express what this was. An acutely schizophrenic patient was improved with the door open, and became for a while more delusional when the door was locked again.

Discussion

Patients' responses to opening the door were determined by whether the patients resided on the open or closed section. Independent observations, interviews, and objective records agree that open section patients and patients slated to be moved to the open area were adversely affected by the unification process. These reactions were apparently the result of a real or fancied loss of status enjoyed by improved patients who were soon to be discharged. Generally, closed section patients were grateful for the freedom and comfort offered by the open door. The three patients who were exceptions had been less involved in transactional processes on the ward and were at the time particularly preoccupied with extra-ward problems.

When the ward was redivided, patient reaction was once agan determined by the patient's location. Those now on the open section were relatively comfortable with the change back. There were explicit objections only from that patient who had most recently been transferred to the open section. Presumably she could not now very easily support the closed door only hours after she had so decidedly denounced it. The patients now on the locked side were adversely affected by the redivision. They interpreted

locking the door as punishment or as ominous or as a loss of freedom.

In general the change was interpreted and appreciated by each patient in relation to his own particular needs. The needs for an "improved" status and freedom were crucial. Although we anticipated that the severely ill patients would be concerned with the protection afforded by the closed door, at no time was this concern evident, and they did quite well with the door open.

Staff Response to Unifying of Ward

The suggestion to unify the ward was made by one of the staff psychiatrists at a weekly team meeting devoted to free discussion of ward problems by the entire staff. At that time the general response of ward personnel was favorable to the change. During the five day period between the meeting and the change, one nurse stated that she felt that the patients would be threatened by the opening of the door. When asked to expand on this, she finally said, "You know you have to consider the staff in this too."

Staff communications after the change focused on the inconvenience of the outer door which frequently had to be opened and shut for traffic. They also mentioned that, without a closed-open ward distinction, patients lack a goal for which to work. Although locking and unlocking the outer door were realistically troublesome, the intensity of the disapproval aroused seemed out of proportion to the difficulty. One nurse stated, "That blasted front door is a pain in the neck." Other nurses said they had trouble keeping track of their patients.

Throughout the 18 days staff members permitted themselves relatively few direct expressions of anger. A nurse who had not been present at the team meeting at which the idea was suggested said rather angrily, "Who decided on the change, anyway?" At a team meeting two weeks after the change, segments of the staff got into an extended, heated, philosophical discussion about the merits of open versus closed wards. At a meeting soon after the initial change, the non-medical staff generally agreed that all patients responded adversely to it. This contradicted nurses' notes and other observations. At the same time much discontent was expressed about patients having to pay for staffs' lunches at picnics. These feelings were ultimately vented on the "administration." One member said, "The hospital should pay for our lunches at these picnics. They certainly can afford it."

During the period of change, the staff psychiatrists who were responsible for the change often made arbitrary and expedient decisions instead of attempting to deal with the feelings underlying staff questions and complaints as was their policy at other times.

Staff Response to Redivision of Ward

Discussion at the group meetings just prior to the redivision concerned the anticipated problems of the change back. Some thought that the closed ward patients would view the locking of the door as punishment, and some staff were concerned at the prospect of being "stuck on the locked ward with sicker patients." Subsequently, the staff became unusually concerned about "acting out," expressing fears of being manipulated by patients, and making demands for more rigid rules to control patient behavior.

Discussion

When the unification proposal was made, the response of the ward personnel was hardly what Stanton and Schwartz[2] call "decision by consensus." The agreement of the staff seemed at the time (and in retrospect certainly was) a "false or partial agreement" made in deference to the rank of the initiator.

Recurrent angry and insecure feelings associated with both changes were expressed in a variety of ways. The inconsistency between the informal oral statements and the more formal nurses' notes suggests that staff members projected their own discomfort onto the patients. The anger expressed during the discussion of the picnic lunch episode became concentrated on the "hospital." The intensity and timing of this anger suggested that the "hospital" meant the decision-making members of the hospital who were responsible for the change. Anxious feelings of staff members were manifested by complaints of being unable to "keep track" of their patients. The con-

scious reference was to keeping track of the patients' physical whereabouts. However, in context, the words seemed to refer to the fact that the staff no longer had a convenient criterion or symbol of patients' improvement (moving to the open ward). Persistent anxiety was subsequently expressed as the recurrent fear that the administrative staff was being manipulated by patients.

The discomfort of the ward personnel, either with the initial change or with the change back, suggests that their response was not to the objective situation but to the manner in which the change was brought about. They had little or no participation in the decision and very little time to adjust to the idea. Hostility and anxiety resulted. In their reactions to these feelings, the psychiatrists did not provide sufficient opportunity for their resolution.

Conclusions

The following hypotheses were suggested by the data:

1. An administrative change may be regarded in different ways by patients and staff.

a. Patients tend to respond to the substance of the change, and appreciate and evaluate it in terms of their own needs, in this case, freedom, comfort, and indication of clinical improvement.

b. Staff members respond primarily to the mechanics of the change, and to the manner in which it is conceived and realized. The extent of their participation and the abruptness of the decision to change a policy are important factors in determining their attitudes.

2. The above has two pragmatic consequences:

a. Patients' reactions to changes in administrative policy should be explored during therapeutic interviews (individual and/or group).

b. Administrative psychiatrists should provide an atmosphere permitting the free expression and understanding of staff feelings before, during and after a policy change. This is especially relevant and important in reference to the "opening" of mental hospitals, the success of which is contingent upon staff attitudes.

(In an article on the institution of such a policy at a large mental hospital, Dr. Herman Snow writes, "The greatest determining factor to opening a ward was the attitude of the nurses and attendants in charge."[5])

3. In a closed-open ward system both patients and staff looked upon transfer to the open section as a sign of "getting well." This attitude sets up a sick-well dichotomy, corresponding to the patient's particular location on the ward. However, a patient should not be moved to an open ward merely on the basis of clinical improvement. The basic purpose, the therapeutic gain, may be compromised by this sick-well distinction.

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Consumption of Mentholated Cigarettes by Alcoholics

WERNER SIMON, M.D., and RUBEL J. LUCERO, M.A.

The authors have observed over a period of time that some of their patients tend to prefer mentholated cigarettes out of proportion to what appears normal consumption. They finally narrowed their "hunch" down to the group of patients who, along with other pathology, suffer from alcoholic and/or drug dependency problems. This study has been made in an effort to validate or disprove this hypothesis.

Method

The authors obtained data on four groups of people: normals, drug dependent individuals, mental patients in general, and alcoholics. All data were gathered during the winter of 1957-58. Although it was possible to gather information from the tobacco industry on the proportion of various types of cigarettes released for sale, it was felt by the authors that a more accurate figure could be obtained from actual sales. Therefore, they gathered data on actual sales, over a month's time, from a drug store, a restaurant, a large grocery store, and a tavern selling only 3.2% beer, obtaining an approximation of the proportion of mentholated cigarettes consumed by the normal population. These data all revealed the same percentage (5%).

The percentage of mentholated cigarettes smoked by drug dependent individuals was obtained from the United States Public Health Service Hospital at Lexington, Kentucky. This figure (5%) represents consumption for the entire winter.

Two state hospitals with a small number (3%) of alcoholics were used as a base to compare with a state hospital having a large concentration (12%) of alcoholics. Since alcoholics enter the treatment center at Willmar State Hospital from all parts of Minnesota, a rural (Fergus Falls) state hospital and an urban (Anoka) state hospital were used jointly. Their respective proportions of mentholated cigarettes sold during the same month were 15% and 13%, which are not reliably different from each other. These percentages were therefore combined.

The percentage of the total of mentholated cigarettes sold in mental hospitals and consumed by alcoholics was arrived at by an algebraic comparison of the differences in alcoholic populations and consumption of mentholated cigarettes in the two different settings. The actual percentage of mentholated versus non-mentholated cigarettes smoked by alcoholics was not obtained. The only way of arriving at this figure, available to the authors, would have been by interview. In view of the obvious unreliability of statements of alcoholics concerning their consumption, it was decided not to use this method. No attempt was made to determine the actual number of cigarettes consumed by the various populations for similar reasons.

TABLE I

Mentholated Cigarettes As a Percentage of Total Cigarettes Consumed

Population	%
Normal	5
Drug Dependent Patients	5
State Hospital with 3% Alcoholics	14
State Hospital with 12% Alcoholics	21
Percentage of Total Mentholated Cigarettes in State Hospitals Consumed by Alcoholics	88

(All differences are statistically significant beyond the .001 level of confidence.)

Results

The data summarized in Table I indicate that alcoholics smoke more mentholated cigarettes than other patients in mental hospitals. They also indicate that alcoholics smoke more mentholated cigarettes than do normals or drug dependent individuals. Normals and drug dependents do not differ from each other in their consumption of mentholated cigarettes. If alcoholics were subtracted from mental hospital populations, the consumption of mentholated cigarettes would be comparable to that of the normal population.

A personal communication from a hospital administrator (Lester E. Johnson, Assistant

From Psychiatry and Neurology Service, Veterans Administration Hospital, Minneapolis, Minnesota, and Willmar State Hospital, Willmar, Minnesota.

Superintendent, Willmar State Hospital) gives further corroborative, though obviously not statistically reliable, information. He states that in at least one southern state, menthol crystals are highly valued as an additive to wine for a more pronounced effect.

Discussion

Although it should be clear from the data, the authors would like to emphasize one point: While it has been established that alcoholics smoke more mentholated cigarettes than others, this does not mean that all people who smoke mentholated cigarettes are alcoholic or even potentially so. It should be further obvious that all alcoholics do not smoke mentholated cigarettes. The data merely indicate a trend that more mentholated cigarettes are consumed by alcoholics than by other members of the population.

Three hypotheses have been advanced in an attempt to explain these results. 1. Oral dependency may play a role. Oral dependency should be found in all psychiatric patients more frequently than in the normal population. Since the data indicate that patients suffering from illnesses other than alcoholism do not smoke more mentholated cigarettes than normals, this hypothesis does not seem tenable. 2. Sensory stimulation may play a part. This would assume a preference for highly seasoned foods, the "taste" of the form of alcohol imbibed, and the strong aromatic quality of mentholated cigarettes. While there may be a relationship between all these, much research needs to be done before one can assume a connection. 3. The third hypothesis has to do with the chemical effects of both menthol and alcohol. Menthol is a central nervous system stimulant, while alcohol is also a temporary stimulant. The two might well have synergistic action producing an augmented effect. The authors are inclined to feel that the third hypothesis may account for the phenomenon described. They are planning an experiment which may help to determine its validity.

Summary

This study evaluates the differential consumption of mentholated cigarettes by four different groups: 1) the normal population, 2) drug dependent individuals, 3) mental hospital patients, and 4) alcoholics.

Conclusions

1. Alcoholics consume more mentholated cigarettes than any other group studied.

2. Mental hospital patients in general, drug dependent individuals, and the normal population smoke about the same proportion of mentholated cigarettes.

3. It is hypothesized that menthol and alcohol have a synergistic effect, which may explain the alcoholic's preference for mentholated cigarettes.

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A NEW GRANT-IN-AID PROGRAM FOR RESEARCH IN ALCOHOLISM AND RELATED SUBJECTS

This is a program through which relatively small research grants may be arranged for competent scientists working in the field of alcoholism.

Licensed Beverage Industries, Inc., has made $500,000 available for a five-year program to meet the growing need for more scientific information both as to the extent of alcoholism and as to its causes and treatment.

The program is administered by a Scientific Advisory Committee whose members represent a wide range of relevant disciplines.

Grants will be awarded to qualified researchers in the biological and behavioral sciences who wish to make preliminary or pilot studies for the purpose of raising or clarifying particularly promising hypotheses.

It is expected that grants will range between $2,000 and $10,000 and that they will run for one year. Renewal of the grant may be considered.

Detailed information and application forms may be obtained by writing to the Scientific Advisory Committee of the Licensed Beverage Industries, Inc., 155 East 44th St., New York 17, N. Y.

Deprol in the Treatment of Depression

PAUL E. GORDON, M.D.

Depression, however distressing, is a universal experience; a normal reaction to the disagreeable facts of life. It becomes abnormal and obsessive when one is not able to divert or transcend this mood, so that normal outlook and behavior are disrupted. Depression is a characteristic feature or leading symptom in many of the psychoses and neuroses, and if not predominant, is commonplace in most disease entities. It is pervasive and predominant in involutional melancholia, the depressed phase of manic depression, reactive depression, climacteric, certain phases of schizophrenia, the anxiety neuroses, and other psychoses.

To the general practitioner, as well as the psychotherapist, depression presents a difficult problem. Relief and release are obtained when the underlying emotional disturbance, or basis in actual pathology, is corrected, and rewarding results are commonly and often unconsciously achieved as rapport between patient and physician becomes established. Michael Balint of London has pointed out that, by far, the most frequently used drug in general practice is the doctor himself.[1]

Admitting the prominence and efficacy of electroconvulsive therapy, and the specific therapies for many pathological entities, recent new drugs are receiving favorable attention in the treatment of the depressed states. These so-called tranquilizers include all drugs which affect the central nervous system, and directly or indirectly influence mood, thought, consciousness, expression and behavior.[1] Meprobamate and benactyzine belong in this category. Experience has shown that many of the tranquilizers actually deepen depression. In this respect meprobamate is superior and unique, for it relieves depression. Likewise, benactyzine hydrochloride possesses antidepressant properties and, like meprobamate, is reportedly unusually low in toxicity and untoward side effects.[2-7] The compound, Deprol, combines 400 mg. meprobamate and 1 mg. benactyzine hydrochloride. It is the use of this compound and adjuvant to psychotherapy which is under consideration in this paper.

The drug, Deprol, used in this study was supplied by Wallace Laboratories, New Brunswick, N. J.

Method

Between March 1957 and July 1959, 50 patients in routine practice were treated with Deprol and the results evaluated (see Table I). Before the introduction of Deprol the majority of the patients in the series were regarded as treatment failures. A few had received no previous drug therapy. The series included the following diagnostic groups: climacteric, anxiety neuroses, reactive depression, neurasthenia, psychoses (senile, postpartum, involutional melancholia), alcoholism, one case with bronchial asthma and another with anginal syndrome.

The daily dosage varied from one to six tablets with the average dose approximately three tablets. The treatment period extended variously from four to 120 days.

Observations

In general, mood and outlook improved as such a variety of symptoms as insomnia, fatigue, irritability, worry, weeping, fear, anorexia, self-reproach, agitation and anxiety were relieved or came under control. Deprol was found very valuable where insomnia was a problem and especially where tension and anxiety were predominant. All but four of the patients were completely relieved of symptoms or greatly improved. They began to sleep well, to enjoy food, to make de-

TABLE I

Males: 19 — Females: 31
Age Range: 18-85 — Average Age: 47
Average Weight: 143
Average Dose: Approximately 3 tablets daily
Average Days of Treatment: 43

Responses:		
Excellent	30	60%
Good	16	32%
Fair	2	4%
Poor	2	4%
Side Effects:		
Drowsiness	7	14%
Dry Mouth	2	4%
Giddiness	2	4%

cisions, and finally, for the most part, to return to normal activity. At least four who had been unable to work returned to their jobs. The drug rendered all patients more amenable to psychotherapy.

Most of the patients tolerated the drug very well, even over long periods. Out of 50, seven complained of drowsiness, two of dryness of the mouth, and two of dizziness, all of which symptoms came under control by reducing the dosage. No other side effects were observed. Since insomnia was present in so many patients, drowsiness as a side effect was not incompatible.

Illustrative Case Histories

Case 1: E.G. This 44-year-old male, suffering from bronchial asthma, peptic ulcer, and anxiety state, displayed severe anxiety, deep depression, and feelings of insecurity. He complained of body tremors, particularly of the hands, which were very noticeable in the morning, and associated with insomnia. As much as six grains of phenobarbital daily, although effective, produced drowsiness, yawning and mental clouding. Deprol was given one tablet three times daily, and one tablet at bedtime. Under this regime the patient obtained remarkable relief and was able to discontinue phenobarbital. He did complain of some daytime drowsiness, which was overcome by adjusting the Deprol dose to one tablet morning and night. To control occasional uneasiness, half a tablet at suppertime sufficed. In his own words: "I have been completely rehabilitated."

Case 2: W.E. This 60-year-old male patient suffering from involutional melancholia, depressed agitated type, with subjective feelings of unworthiness, insecurity, and loss of family affection; was severely depressed, could not sleep, and was unkempt and slovenly in his personal habits. He refused to eat, became tearful, and accusatory in speech. Male sex hormones were administered, and Deaner was given to relieve depression. He became more amenable to psychotherapy, and more cleanly in personal habits. However, the intractable insomnia continued, and he complained of restlessness during the day with extreme fatigue. Two tablets of Deprol at bedtime permitted the patient eight hours of restful sleep, promoting recovery to the point that all therapy except Deprol was discontinued. He is back at work, and says he feels fine.

Case 3: G.Y. This 55-year-old male patient, suffering from angina pectoris, postcholecystectomy syndrome, and severe depression, complained of anginal pain following nervous upsets and after meals; also of frequent frightening dreams, often awakening with anginal pain, so that he became afraid to sleep. The patient appeared highly emotional and extremely tense. Seconal and Nembutal were tried but each accentuated the nightmares and increased the concomitant anginal attacks. With one Deprol tablet at bedtime the patient had, for the first time in two years, a restful night of sleep; ½ tablet three times daily suppressed anxiety. The angina came under control, so that he could be maintained on 20 mg. Peritrate three times daily.

TABLE II

Analysis of Clinical Data

				Results				MEDICATION Previous		Deprol	
Diagnosis	Total	Male	Female	E	G	F	P	None	Unsuccessful	Alone	With Other
Climacteric	14	2	12	10	2	1	1	1	13	11	3
Anxiety Neuroses	14	7	7	9	3	1	1	3	11	11	3
Reactive Depression	7	1	6	3	4			1	6	3	4
Neurasthenia	6	5	1	3	3			1	5	5	1
Psychoses	5	2	3	2	3			3	2	2	3
Senile	2	1	1		2			1	1	2	
Involutional Melancholia	2	1	1	1	1			1	1		2
Postpartum	1		1	1				1			1
Alcoholism	2	1	1	1	1				2	1	1
Bronchial Asthma	1		1	1					1		1
Anginal Syndrome	1	1		1					1		1
Total	50	19	31	30	16	2	2	9	41	33	17

E—excellent—indicates complete remission of symptoms.
G—good—indicates definite improvement without complete control of symptoms.
F—fair—indicates equivocal results.
P—poor—indicates no remission of symptoms, or relapse to original status, following some improvement while on therapy.

TABLE III

Individual Patient Analysis

No.	Age	Sex	Weight	Diagnosis	Previous Therapy	Concomitant Therapy*	Deprol Dose	Duration in Days	Response
CLIMACTERIC GROUP:									
1	46	F	136	Menopause	Estrogen, Barbiturates	None	2 TID	45	P
2	50	F	182	Menopause	Hormones, Sedation	None	1 HS 1 PRN	89	E
3	47	F	129	Menopause	Estrogen, Dexamyl	None	1 Q6H (TID)	28	E
4	47	F	126	Menopause	Estrogen, Butisol	None	1 Q6H (TID)	90	E
5	47	F	109	Menopause	Estrogen	Sedation	½ TID 1 BID	45	E
6	59	M	118	Climacteric	Male Hormones, Ephedrine	None	1 Q6H (TID)	30	E
7	47	F	118	Menopause	Peritrate, Sedation	None	½ TID 2 HS	73	E
8	47	F	158	Menopause	Estrogen	None	1 Q6H (TID)	75	E
9	42	F	118	Menopause	Estrogen	Phenobarbital	½ TID 1 HS	55	E
10	56	F	210	Menopause	KSCN Phenobarbital	Amphetamine	1 TID	50	G
11	51	M	173	Climacteric	Male Hormones	None	1 Q6H (TID)	30	G
12	52	F	156	Menopause	Anti-hypertensives	Estrogen	1 Q6H (TID)	13	E
13	54	F	120	Menopause	Refused	None	1 Q6H (TID)	60	F
14	51	F	149	Menopause	Estrogen, Hypnotics	None	1 HS	30	E
ANXIETY NEUROSES GROUP:									
15	67	M	135	Anxiety State	Hypnotics	Liver and Iron	2 HS ½ PRN	60	E
16	41	M	155	Chronic Anxiety Neurosis	Phenobarbital, Miltown	None	1 TID	30	E
17	30	F	121	Severe Anxiety State	Equanil, Compazine	None	½ TID	11	G
18	61	M	160	Anxiety State	Phenobarbital	Peritrate	½ TID 1 PRN 1 HS	120	E
19	21	F	116	Severe Anxiety State	Phenobarbital, Atropine	None	1 Q6H (TID)	30	G
20	70	M	185	Anxiety State	Banthine, Phenobarbital	Ulcer Therapy	1 Q6H (TID)	60	F
21	39	F	118	Free-floating Anxiety	Equanil, Phenothiazines	Estrogen	1 TID ½ BID	30	P
22	44	M	180	Severe Anxiety State	Barbiturates, Tedral	None	1 TID 1 HS	14	E
23	52	M	135	Anxiety State	Sedation, Analgesics	None	1 TID	54	E
24	35	F	106	Anxiety Reaction with Depression	None	None	½ TID ½ PRN 1 HS	30	E
25	75	F	98	Anxiety State	Rauwolfia, KSCN	Barbiturates	½ TID 1 BID	30	E

*Other than psychotherapy.

No.	Age	Sex	Weight	Diagnosis	Previous Therapy	Concomitant Therapy*	Deprol Dose	Duration in Days	Response
26	35	F	126	Anxiety Reaction	None	None	1 TID	25	E
27	39	M	160	Severe Anxiety Neurosis	None	None	1 TID	30	G
28	28	F	116	Anxiety State	Barbiturates	None	1 Q6H (TID)	30	E
REACTIVE DEPRESSION GROUP:									
29	63	M	165	Reactive Depression	Ultran, Phenobarbital	None	½ TID	60	E
30	34	F	152	Reactive Depression	Phenobarbital	None	1 Q6H (TID)	17	G
31	34	F	175	Reactive Depression	Psychotherapy	Meprobamate	1 Q6H (TID)	14	G
32	35	F	126	Reactive Depression	Cortisone, Sedatives	Dental Care	1 TID	60	G
33	30	F	106	Reactive Depression	None	Liver and Iron	1 TID	14	E
34	37	F	132	Reactive Depression	Psychotherapy, Dexamyl	Marsilid	1 Q6H (TID)	12	G
35	47	F	135	Reactive Depression	Anti-hypertensives, Reserpine	None	1 TID 1 HS 1 PRN	60	E
NEURASTHENIA GROUP:									
36	32	M	156	Neurasthenia	Phenobarbital, Psychotherapy	None	1 HS	58	G
37	32	M	160	Neurasthenia	Barbiturates, Antispasmodics	Belladonna	1 BID 1 HS	50	E
38	26	M	120	Severe Neurasthenia	Dilantin, Phenobarbital	None	1 PRN 2 HS	50	E
39	40	M	198	Neurasthenia, Hypochondriasis	Sedation, Antispasmodics	None	1 PRN	14	G
40	79	F	118	Neurasthenia with Anxiety	None	None	1 QID	21	G
41	35	M	120	Neurasthenia	Barbiturates, Vitamins	None	½ BID 1 PRN	120	E
PSYCHOSES GROUP:									
42	24	F	128	Postpartum	Shock Therapy	None	2 HS	14	E
43	85	F	107	Senile	None	None	½ TID	50	G
44	68	M	132	Senile	None	Vitamins	1 BID ½ PRN 1 HS	34	G
45	60	M	169	Involutional Melancholia	Male Hormones	Anti-hypertensives	1 Q6H 2 HS	120	E
46	55	F	165	Involutional Melancholia	None	Estrogen, Frenquel	½ TID 1 PRN 2 HS	30	G
MISCELLANEOUS GROUP:									
47	66	M	212	Alcoholism	Dartal	Vitamins	1 TID 2 HS	60	E
48	50	F	148	Alcoholism	Vitamins, Barbiturates	None	1 Q6H (TID) 2 HS	50	G
49	18	F	122	Bronchial Asthma	Antihistamines, Ephedrine	Same	1 BID	60	E
50	55	M	182	Anginal Syndrome	Cholecystectomy	Peritrate, Barbiturates	½ TID 1 HS	7	E

*Other than psychotherapy.

Case 4: E.A. This 66-year-old former policeman (now salesman) had become alcoholic, following the loss of his wife six years before, and was exceedingly depressed, apprehensive, nervous, and unable to sleep. He found that alcoholic beverages had a soothing effect on his "nerves," and resorted to it in increasing amounts. Eventually even large amounts of alcohol failed to placate and he sought medical help. Deprol was given, initially ½ tablet three times daily, and one at bedtime. The dose was later increased to one tablet three times daily and two at bedtime. While on this regime, and except for an "occasional beer," he stopped all alcohol in other forms. This treatment was followed for two months, and he is being maintained satisfactorily on one tablet of Deprol when necessary.

Case 5: M.P. This 39-year-old female suffering from early menopause and free-floating anxiety and depression, had multiple somatic complaints including irregular menses with hot flashes, sweats, vertigo, tearfulness, and extreme lability. Although estrogen relieved the menopausal symptoms, it did not lessen the anxiety or depression. Psychotherapy was not really successful, since the relief of one somatic complaint was replaced immediately by another. The phenothiazine drugs, meprobamate and Deprol failed to help this patient and it appears that involutional psychosis is imminent.

Summary

Fifty patients in private practice with severe depression and insomnia, who were suffering from a variety of disorders, received Deprol (meprobamate combined with benactyzine hydrochloride) as adjuvant to psychotherapy. All but five showed definite improvement, and many had complete remission of symptoms on this medication.

Deprol was found to facilitate psychotherapy.

There were no serious or untoward side effects, and such complaints as drowsiness, dryness of mouth, and giddiness were relieved by lowering the dosage. Drowsiness, in a series where so many complained of insomnia, was not an altogether unwelcome side effect.

Conclusion

Deprol is an excellent adjunct to psychotherapy, and is recommended in the treatment of the depressed states, especially where anxiety and insomnia are troublesome components.

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A Combination Sedative in Emotionally Disturbed Office Patients

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During the past two years there has been an increasing interest in psychotherapeutic agents. Tranquilizers and ataractics have supplanted many of the sedative-hypnotic drugs commonly used in treatment. Nevertheless, there is a definite place for use of sedative medications.

Psychosomatic and psychoneurotic patients represent a therapeutic problem for every clinician. Some of these are referred for care to psychiatrists, but the great majority remain the responsibility of the internist and general practitioner. As Batterman et al.[1] have pointed out, it is pharmacologically unsound to expect any one drug to combat overactivity of the central nervous system at all possible levels of reactiveness. For this reason, based upon studies by Reinhard et al.,[2] and Brodie and his associates,[3] various therapeutic combinations were proposed to act upon several segments of the central nervous system. Batterman et al.[1] used such a formulation of acetylcarbromal, mephenesin and reserpine as a sedative with a resultant effectiveness of 80%.

Acetylcarbromal was found to act subcortically; reserpine, hypothalamically; and mephenesin, supraspinally. We, therefore, decided to use a mixture of these drugs to treat a variety of psychoneurotic and psychosomatic ills seen in office practice.

Method

Tablet mixtures of acetylcarbromal 200 mg.; mephenesin, 150 mg.; and reserpine, 0.05 mg. were administered to 166 ambulatory patients. The study comprised 118 women and 48 men, average age 42.03 years. Age span was 15 to 91 years. Median age was 43 years.

Results of treatment with Amril were classified according to the following rigid criteria:

Complete Relief: Those patients who became symptom free, regaining positive control of their emotional problems.

Major Relief: Those patients who after treatment obtained significant relief of symptoms. While not asymptomatic, they appeared better equipped to face their emotional disturbances.

Slight Relief: Those patients displaying sporadic, but only mild reduction in their symptomatology.

None: Those patients displaying little or no significant improvement.

When Amril was used as a sedative and hypnotic, dosage ranged from one tablet daily to one tablet four times a day. Occationally, two tablets were administered three times a day. For its hypnotic effect the combination was given at bedtime in a dosage ranging from one to four tablets. Treatment time extended from a minimum of one week to a maximum of 12 weeks. These periods of therapeutic trial were felt to be adequate for a meaningful evaluation.

Results

Using the above criteria we found complete relief in 60 patients; 52 patients developed major improvement with marked decrease of their emotional and psychosomatic symptoms; the remainder showed slight or no benefits. (Table I.)

A summary of the symptom-complex with the results occurring in each is tabulated in Table II.

Side effects were noted in 34 patients. The majority of these untoward reactions were slight and not of sufficient degree to warrant discontinuing the medication. Most of the side effects were of gastro-intestinal origin, consisting of nausea, heartburn, indigestion and flatulence. There were several cases of slight drowsiness, one case of slight dizziness, one patient complained of dryness of the mouth, and one patient erupted with a macular rash.

The formulation used in this study was kindly supplied by Amfre-Grant, Inc., Brooklyn, New York, and is sold on the market as Amril Tablets.

TABLE I

Results of Treatment with Amril

Patient No.	Sex	Age	Diagnosis	Dosage	Duration of Therapy	Therapeutic Effects	Side Effects
1	F	50	Anxiety Tension	1 t.i.d.	6 weeks	Major	None
2	F	40	Acute Depression	1 t.i.d. 2 h.s.	9 weeks	Complete	None
3	F	56	Hypochondria	1 t.i.d. 2 h.s.	8 weeks	Major	None
4	M	55	Anxiety Tension	1 t.i.d. 2 weeks- 2 t.i.d.	7 weeks	Complete	None
5	F	36	Anxiety Tension	1 t.i.d. 3 weeks- 1 q.i.d.	6 weeks	Major	None
6	F	65	Anxiety Tension	1 t.i.d.	8½ weeks	Slight	G.I. Symptoms
7	F	36	Anxiety Tension	1 t.i.d. 5 weeks- 1 t.i.d. 2 h.s.	7½ weeks	Major	None
8	F	25	P.N. Mixed Type	1 t.i.d. 5 weeks 1 t.i.d.	7 weeks	Slight	None
9	F	40	Anxiety Tension	1 t.i.d.	8 weeks	Major	None
10	F	41	Acute Depression	1 t.i.d. 5 weeks- 2 h.s.	8 weeks	Major	None
11	F	33	Anxiety Tension	1 b.i.d.	9 weeks	Major	None
12	F	57	Hypochondria	1 q.i.d.	5 weeks	None	None
13	F	27	Anxiety Tension	1 q.i.d.	2 weeks	Major	None
14	F	42	Anxiety Tension	1 t.i.d.	5 weeks	Major	None
15	F	30	Anxiety Tension	1 t.i.d. 2 weeks- 2 h.s.	6½ weeks	Complete	None
16	F	48	Anxiety Tension	3 h.s.	8 weeks	Complete	None
17	M	30	P.N. Mixed Type	1 t.i.d.	7 weeks	None	G.I. Symptoms
18	F	23	Anxiety Tension	2 h.s.	7½ weeks	Complete	None
19	M	66	Anxiety Tension	2 h.s.	8 weeks	Complete	None
20	F	60	P.N. Mixed Type	1 t.i.d.	5 weeks	None	None
21	F	35	Hypochondria	1 t.i.d. 2 h.s.	5 weeks	None	None
22	F	47	Anxiety Tension	1 t.i.d.	7 weeks	Major	None
23	F	43	Menopausal Syn.	1 t.i.d.	3½ weeks	Slight	Nausea
24	M	15	Anxiety Tension	1 t.i.d.	4 weeks	Major	None
25	M	58	Anxiety Tension	1 t.i.d.	6½ weeks	Major	None
26	F	38	Anxiety Tension	1 t.i.d. 2 h.s.	9 weeks	Major	None
27	F	40	Anxiety Tension	1 q.i.d.	8 weeks	None	None
28	M	67	Anxiety Tension	1 t.i.d.	6 weeks	Major	None
29	F	55	P.N. Mixed Type	1 t.i.d.	6½ weeks	Slight	None
30	M	24	Anxiety Tension	1 b.i.d. 2 h.s.	2½ weeks	Complete	None
31	F	50	Anxiety Tension	1 b.i.d.	12 weeks	Major	None
32	F	21	P.N. Mixed Type	1 q.i.d. 3 weeks- 1 t.i.d.	5 weeks	Major	None
33	M	37	Anxiety Tension	1 t.i.d.	5½ weeks	Major	None
34	F	43	Anxiety Tension	1 q.i.d.	4 weeks	Major	Nausea
36	M	33	Anxiety Tension	1 b.i.d.	8 weeks	Major	None
36	F	41	Anxiety Tension	1 q. day 2 h.s.	1 week	None	None

Patient No.	Sex	Age	Diagnosis	Dosage	Duration of Therapy	Therapeutic Effects	Side Effects
37	F	31	Anxiety Tension	1 q.i.d.	5 weeks	Slight	None
38	F	40	Anxiety Tension	2 h.s.	4 weeks	Complete	None
39	M	41	Anxiety Tension	1 b.i.d.	6 weeks	Complete	None
40	F	45	Hypochondria	1 t.i.d.	4 weeks	None	None
41	M	28	Anxiety Tension	1 t.i.d.	5 weeks	Complete	None
42	F	49	Anxiety Tension	1 t.i.d.	6 weeks	Slight	G.I. Symptoms
43	F	50	Anxiety Tension	2 h.s.	7 weeks	Complete	None
44	F	29	Anxiety Tension	1 b.i.d. 2 h.s.	6 weeks	Major	None
45	F	31	Anxiety Tension	2 h.s.	8 weeks	Complete	None
46	F	33	Anxiety Tension	1 t.i.d.	6 weeks	Complete	None
47	F	33	Anxiety Tension	1 t.i.d.	5½ weeks	Complete	None
48	F	22	Anxiety Tension	1 q.i.d.	5 weeks	Major	None
49	F	23	Hysteria	1 t.i.d. 2 h.s.	2 weeks	None	None
50	M	42	Anxiety Tension	1 t.i.d. 2 h.s.	6 weeks	Complete	None
51	F	43	Hypochondria	1 t.i.d. 3 weeks- 2 t.i.d. 2 h.s.	6 weeks	None	G.I. Symptoms
52	F	33	Anxiety Tension	1 q.i.d.	4 weeks	Major	G.I. Symptoms
53	M	35	Anxiety Tension	1 q. day	5 weeks	Complete	None
54	M	57	Anxiety Tension	2 h.s.	4 weeks	Complete	None
55	F	49	Anxiety Tension	1 t.i.d. 2 h.s.	4 weeks	Major	None
56	F	34	Anxiety Tension	1 q.i.d.	4 weeks	Complete	None
57	M	27	Anxiety Tension	1 t.i.d.	4 weeks	Major	Nausea
58	F	31	Anxiety Tension	1 q.i.d.	4 weeks	Major	G.I. Symptoms
59	M	50	Anxiety Tension	1 t.i.d. 2 h.s.	4 weeks	Slight	None
60	F	31	Hypochondria	1 q. day 2 h.s.	4 weeks	None	None
61	F	25	Neurocirculatory Asthenia	1 q.i.d. 3 weeks- 1 t.i.d.	8 weeks	Major	Nausea on 1 q.i.d.
62	F	32	Anxiety Tension	1 t.i.d. 2 h.s.	6 weeks	Slight	G.I. Symptoms
63	F	46	Hypochondria	1 q.i.d. 1 week- 2 t.i.d. 3 h.s. 2 weeks- 2 b.i.d. 3 h.s.	5 weeks	Slight	G.I. Distress
64	M	51	Anxiety Tension	1 q.i.d.	6 weeks	Complete	None
65	F	20	Anxiety Tension	1 qam 2 h.s.	5 weeks	Complete	None
66	F	21	Anxiety Tension	1 t.i.d. 2 h.s.	5 weeks	Complete	None
67	F	29	Anxiety Tension	2 t.i.d.	5 weeks	Major	None
68	F	32	Anxiety Tension	1 q.i.d.	5 weeks	Major	None
69	F	43	Anxiety Tension	2 h.s.	4 weeks	Complete	None
70	M	68	Alcoholism	1 b.i.d. 2 h.s.	4 weeks	None	None
71	M	65	Anxiety Tension	1 b.i.d. 2 h.s.	5 weeks	Complete	None
72	F	36	Anxiety Tension	1 q.i.d.	3½ weeks	Slight	None
73	M	36	Anxiety Tension	1 t.i.d.	6 weeks	Major	None
74	F	46	Hysteria	1 t.i.d. 2 h.s.	4 weeks	None	None

Patient No.	Sex	Age	Diagnosis	Dosage	Duration of Therapy	Therapeutic Effects	Side Effects
75	F	38	Senile Dementia	2 h.s.	3 weeks	Complete	None
76	F	72	Senile Dementia	2 h.s.	5 weeks	Complete	None
77	F	37	Menopausal Syn.	1 q.i.d.	6 weeks	Major	None
78	M	60	Anxiety Tension	2 h.s.	5 weeks	Complete	None
79	F	53	Anxiety Tension	3 h.s.	5 weeks	Slight	None
80	M	37	Anxiety Tension	1 q.i.d.	5 weeks	None	None
81	F	55	Insomnia Secondary	2 h.s.	5 weeks	Complete	None
82	M	30	Anxiety Tension	1 b.i.d. 2 h.s.	4 weeks	Complete	None
83	F	34	Anxiety Tension	2 h.s.	4 weeks	Complete	None
84	F	48	Anxiety Tension	2 h.s.	4 weeks	Complete	None
85	M	56	Anxiety Tension	1 b.i.d. 2 h.s.	5 weeks	Complete	None
86	F	17	Anxiety Tension	1 b.i.d. 2 h.s.	5 weeks	Complete	G.I. Symptoms
87	F	78	Ch. Depression	2 h.s.	4½ weeks	Complete	None
88	F M	37	Premenstrual Tension	1 t.i.d. 6 days before period	6 days prior to 2 periods	Complete	None
89	F	40	Hypochondria	1 t.i.d. 2 h.s.	3 weeks	None	None
90	M	60	Anxiety Tension	1 t.i.d.	4 weeks	Complete	None
91	F	55	P.N. Mixed Type	1 b.i.d. 2 h.s.	5½ weeks	Major	None
92	F	26	Acute Reactive Depression	1 q.i.d.	4 weeks	Slight	None
93	F	50	Neurocirculatory Asthenia	1 t.i.d.	4 weeks	None	None
94	F	30	Anxiety Tension	1 t.i.d. 2 h.s.	1 week	None	None
95	F	50	Menopausal Syn.	1 h.s.	8 weeks	Complete	None
96	F	40	Hypochondria	1 t.i.d. 2 h.s.	3 weeks	None	None
97	F	46	Menopausal Syn.	2 h.s.	7½ weeks	Complete	None
98	F	48	Anxiety Tension	1 t.i.d. 2 h.s.	6 weeks	Slight	None
99	M	42	Anxiety Tension	1 t.i.d. 2 h.s.	1 week	None	G.I. Symptoms
100	F	39	Anxiety Tension	1 t.i.d. 2 h.s.	6 weeks	Complete	Complete
101	M	68	Anxiety Tension	1 b.i.d. 2 h.s.	2 weeks	None	None
102	F	32	Hypochondria	1 t.i.d. 2 h.s.	7 weeks	Slight	None
103	M	56	Alcoholism	1 q.i.d.	8 weeks	Major	None
104	F	50	Menopausal Syn.	1 q.i.d.	3 weeks	None	G.I. Symptoms
105	F	48	Acute Reactive Depression	2 h.s.	7 weeks	Complete	None
106	F	24	Anxiety Tension	1 b.i.d. 2 h.s.	9 weeks	Major	None
107	F	40	Anxiety Tension	1 t.i.d. 2 h.s.	3 weeks	Complete	None
108	M	56	Anxiety Tension	1 t.i.d. 2 h.s.	3 weeks	Complete	None
109	F	50	Anxiety Tension	2 h.s.	2 weeks	Complete	None
110	F	59	Anxiety Tension	1 b.i.d. 2 h.s.	6 weeks	None	None
111	F	75	Anxiety Tension	2 h.s.	4 weeks	Major	None
112	F	59	Anxiety Tension	1 t.i.d.	6 weeks	Slight	None

Patient No.	Sex	Age	Diagnosis	Dosage	Duration of Therapy	Therapeutic Effects	Side Effects
113	M	48	Anxiety Tension	1 q. day 2 h.s.	6 weeks	Complete	None
114	M	60	Anxiety Tension	1 to 4 hs.	5 weeks	None	Nausea
115	M	72	Anxiety Tension	1 t.i.d. 2 h.s.	5½ weeks	Slight	None
116	M	29	Anxiety Tension	1 b.i.d. 2 h.s.	4 weeks	Slight	None
117	M	73	Anxiety Tension	2 h.s.	4 weeks	Complete	None
118	F	32	Anxiety Tension	1 b.i.d. 2 h.s.	4 weeks	Major	Macular Rash
119	F	29	Anxiety Tension	2 h.s.	5 weeks	Complete	None
120	M	42	Alcoholism	2 h.s.	2½ weeks	None	None
121	M	53	Hypochondria	1 t.i.d.	2 weeks	Slight	None
122	F	39	Premenstrual Tension	2 h.s. 6 days before period	6 days prior to 5 periods	Complete	None
123	M	60	Anxiety Tension	2 h.s.	5 weeks	Complete	None
124	F	53	Anxiety Tension	1 t.i.d.	3 weeks	None	None
125	F	37	Anxiety Tension	1 t.i.d. 2 h.s.	4 weeks	Major	None
126	F	27	Acute Reactive Depression	1 t.i.d. 2 h.s.	3 weeks	Major	None
127	F	58	Anxiety Tension	2 h.s.	1 week	Major	None
128	F	24	Anxiety Tension	1 q.i.d.	4 weeks	Major	None
129	M	27	Neurocirculatory Asthenia	1 q.i.d.	4 weeks	Slight	None
130	M	35	Anxiety Tension	1 q.i.d.	6 weeks	Major	None
131	F	28	Hysteria	1 q.i.d.	1 week	Slight	None
132	F	28	Anxiety Tension	1 q.i.d.	8 weeks	Slight	Drowsiness
133	M	27	Anxiety Tension	1 q.i.d.	1 week	Complete	None
134	F	45	Hysteria	1 q.i.d.	4 weeks	Complete	Drowsiness
135	F	38	Menopausal Syndrome	1 q.i.d.	8 weeks	Major	None
136	F	28	Anxiety Tension	1 q.i.d.	2 weeks	Major	Drowsiness
137	F	37	Anxiety Tension	1 q.i.d.	4 weeks	Major	None
138	F	38	Neurocirculatory Asthenia	1 q.i.d.	8 weeks	Major	None
139	F	34	Hysteria	1 q.i.d.	2 weeks	Major	None
140	F	46	Menopausal Syn.	1 q.i.d.	4 weeks	Major	Drowsiness
141	M	36	Anxiety Tension	2 h.s.	4 weeks	Major	None
142	M	59	Acute Reactive Depression	1 q.i.d.	5 weeks	Major	None
143	M	34	Anxiety Tension	1 h.s.	2 weeks	Complete	None
144	M	46	Anxiety Tension	1 q.i.d.	2 weeks	Complete	None
145	M	36	Neurocirculatory Asthenia	1 q.i.d.	4 weeks	Major	None
146	M	64	Anxiety Tension	1 b.i.d.	7 weeks	Major	None
147	F	91	Anxiety Tension	2 h.s.	8 weeks	Major	None
148	F	67	Anxiety Tension	2 q.i.d.	8 weeks	Slight	None
149	F	30	Anxiety Tension	2 h.s.	8 weeks	Major	None
150	F	35	Anxiety Tension	1 b.i.d. 2 h.s.	4 weeks	Complete	None
151	F	30	Anxiety Tension	1 q.d. 2 h.s.	4 weeks	Complete	None
152	F	35	Anxiety Tension	3 h.s.	1 week	None	None
153	F	30	Anxiety Tension	2 h.s.	2½ weeks	None	None
154	F	38	Menopausal Syn.	2 q. day	3 weeks	None	None
155	F	63	Anxiety Tension	2 h.s.	1 week	Complete	None
156	F	35	Anxiety Tension	2 h.s.	3 weeks	Complete	None
157	F	27	Hypochondria	2 h.s.	1 week	Complete	None
158	M	50	Anxiety Tension	2 h.s.	4 weeks	Complete	None

Patient No.	Sex	Age	Diagnosis	Dosage	Duration of Therapy	Therapeutic Effects	Side Effects
159	F	40	Anxiety Tension	1 q.i.d.	6 weeks	Slight	None
160	F	31	Anxiety Tension	1 q.i.d.	4 weeks	None	None
161	F	34	Anxiety Tension	1 t.i.d. 2 h.s.	4 weeks	Complete	None
162	M	47	Anxiety Tension	2 - 4 h.s.	6 weeks	Major	None
163	F	38	Anxiety Tension	1 q.i.d.	5 weeks	Major	None
164	F	34	Anxiety Tension	1 t.i.d. 2 h.s.	5 weeks	Major	None
165	F	60	Anxiety Tension	2 h.s.	4 weeks	Complete	None
166	F	37	Anxiety Tension	1 t.i.d. 2 h.s.	2 weeks	Complete	None

TABLE II

Results Classified by Diagnosis

Diagnosis	*Therapeutic Effects*			
	Complete	Major	Slight	None
Anxiety Tension	46	39	15	10
Acute Depression	2	2	1	1
Chronic Depression	1	2	2	1
Senile Dementia	2	0	0	0
Hypochondria	1	1	3	7
Psychoneurosis, Mixed Type	0	2	2	2
Menopausal	2	3	1	2
Hysteria	1	1	1	2
Neurocirculatory Asthenia	0	3	1	1
Alcoholism	0	1	0	2
Insomnia Due to Drug	1	0	0	0
Premenstrual	2	0	0	0

118 Women — 48 Men

We found the drug of great value in the relief of anxiety symptoms, in that it produced a sensation of relaxation, calmness, and a feeling of greater emotional control. Patients on this therapy did not complain of daytime drowsiness or loss of alertness.

Summary

A series of 168 patients suffering from emotional disturbances were studied in a typical office practice. They were treated with a sedative-hypnotic mixture consisting of a combination of acetylcarbromal, mephenesin and reserpine for a period extending from one to 12 weeks. Of these, 66.6% received complete or major therapeutic effects, 21.4% were benefited slightly, and 16.6% showed no therapeutic benefit. While side effects were noted in 34 patients or 20.2%, the majority of these reactions were slight and not of sufficient degree to warrant discontinuing the medication. It has been our observation that the drug is an effective sedative and has the advantage in many patients, previously on barbiturates, of not causing drowsy daytime sluggishness.

Conclusion

It is pharmacologically unsound to expect any one drug to combat overactivity of the central nervous system at all possible levels of reactiveness. Amril®, a combination of acetylcarbromal, mephenesin and reserpine, each of which acts upon several segments of the central nervous system has proven to be a satisfactory and safe sedative-hypnotic mixture in the treatment of a variety of emotional disturbances found in an office practice. Of that total treated 66.6% showed complete or major improvement. This drug seems to be a valuable addition to the many psychotherapeutic agents available to the clinician.

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Electroencephalographic Abnormalities and Psychiatric Manifestations in Intermittent Porphyria

Z. S. SIKES, M.D.

Two cases of acute intermittent porphyria which showed electroencephalographic changes during the acute porphyric crises have been diagnosed and studied. These changes appeared to be in direct relation to the severity of the attack. This disease with more faces than Eve should be kept in mind by all practitioners of the healing art since the histories in many cases show a multitude of inaccurate diagnoses even covering periods of many years.

Acute porphyria usually appears in adults, is a chronic disease occurring in acute episodes after symptomless intervals of months to years. Such an episode may begin with abdominal pain, neurologic or mental symptoms and it is often, but not necessarily, accompanied by voiding of dark or maroon colored urine. This is truly a disease of protean symptomatology, showing all or various combinations of colicky abdominal pains, nausea and vomiting, constipation, ileus, jaundice, fever, leucocytosis peripheral neuritis, paralysis, muscle atrophy, neurotic behavior delirium, psychosis and convulsions. Thus the disease has been mistaken for acute appendicitis, surgical ileus, cholecystitis, ovarion cyst, ectopic pregnancy, conversion or anxiety reaction, schizophrenia and psychopathic personality. Nesbitt[26] has made an extensive review of the literature and pointed out the neglect of this disease in medical teaching in spite of the fact that many cases are reported. Cross[6] makes a plea for psychiatrists to be on the alert and to suspect porphyria when a combination of abdominal pain, neurotic or schizophrenic behavior and neurological symptoms are seen. Walter[36] describes a case who had four surgical procedures performed prior to diagnosis. Hysterical behavior, manic-depressive and Korsakoff's psychosis pictures are cited by Watson.[39] Neurologic manifestations are described by Gilbert et al.,[14] Kiloh and Nevin,[22] Abraham et al.,[2] Abbott and Evans[1] and Hoagland.[19] Eliaser and Kondo[10] and Walter[36] describe electrocardiographic changes in the disease. Jorgensen and With[21] show clearly a universal distribution of the disease and also call for physicians, surgeons, psychiatrists and neurologists to be on the alert for its diagnosis.

The disease is characterized by the variable presence in the urine of coproporphyrin, uroporphyrin and porphobilinogen. The urine may not show a port-wine color often described as characteristic. In fact, Turner[35] states that most of the color of the urine when present is due to a pigment which has been called urofuocin, rather than to porphyrin. He adds further that porphyrin excretion may be present even during periods of symptomatic remission. Mason et al.[25] noted that the excretion of porphyrin may cease during an attack. According to Schwartz[34] a positive test for porphobilinogen in the urine is considered pathognomonic of porphyria. The presence of porphobilinogenuria is determined by the Watson and Schwartz test.[38]

Case Reports

Case No. 1 was admitted to the Psychiatric Service 7/22/55 with complaints of abdominal pains, insomnia, and severe nervousness. He had suffered from periodic attacks of epigastric pain and cramping, nausea, vomiting, and sometimes diarrhea. While in service there were many sick calls for gastrointestinal symptoms. A review of his service record showed other complaints to be similar to the present and as a result he was discharged and ultimately service connected for anxiety state with psychosomatic complaints. At home he was diagnosed as having duodenal ulcer. The impression of sinusitis led to a window being cut in a maxillary sinus without relief. He had trouble concentrating.

On admission to our hospital physical examination was negative. X-ray of chest negative, gastrointestinal series failed to confirm the presence of a duodenal ulcer. Skull films were negative. Complete blood count and blood serology negative. NPN 26 milligrams percent, fasting blood sugar 80 milligrams percent, cholesterol 160 milligrams percent. Mental examination revealed a bizarre picture. His conversation was vague and rambling. The affect was inappropriate and he often laughed when telling how badly he felt. During the physical examination he suddenly sat back in the chair and closed

his eyes for a full minute. He could not explain this episode, saying only he felt either confused or afraid.

On the ward he was restless, anxious and apprehensive, and showed many episodes of "blocking," being blank for a few seconds to a full minute. There was impairment of memory especially for recent events. There was a marked tendency to dramatize his symptoms. At other times he was perfectly clear, expressing himself as feeling well, and during such periods his behavior was not unusual. Two lumbar punctures were done, with normal pressure, dynamics and laboratory findings. A freshly voided specimen of urine was light amber in color but on exposure to light it rapidly changed in color to a deep mahogany to dark brown.

The Watson-Schwartz test for porphobilinogen was strongly positive, and there was reddish fluorescence under the Wood's lamp. Psychological evaluation included the Wechsler-Bellevue, Rorschach and Bender-Gestalt, and these tests revealed gross personality disorganization, inadequate defenses loose enough to indicate some psychotic behavior, pronounced confusion and flight of ideas; similarities to catatonic, hysterical and dissociative personality reactions were seen but the weight of evidence suggests such responses were due to organic cortical insult. An electroencephalogram was requested because of the organic signs clinically and psychologically. This showed an abnormally slow (diffuse) record with many waves in the 5 to 7 per second range. Voltages were moderately increased and became further elevated with hyperventilation. Mild bursts of slowing were noted in the fronto-parietal regions during hyperventilation. In addition to the diffuse abnormality there was intermittent localized slowing of moderate degree in the left temporal area. Abnormal EEG compatible with acute toxic encephalitis.

The patient's hospital course was stormy, with progression to invalidism, severe neurological involvement which was upper motor neuron type rather than flaccid. The clinical picture now was quite organic, with severe mental confusion, helplessness, hyperactive tendon reflexes with preservation of the abdominals, positive Hoffman and Babinski signs bilaterally and increased muscle tonus. Treatment with intravenous calcium gluconate, ACTH and parenteral vitamins in large doses produced no change. Meperidine hydrochloride was required for relief of abdominal pain. The temperature frequently spiked to 103 degrees, and although there was no leucocytosis the eosinophil count was elevated during such febrile periods to as high as 14 per cent. With continued support and relief of pain and intravenous fluids, there was apparently spontaneous remission with fairly rapid clearing of the mental picture, disappearance of the pyramidal tract signs but with mild retention of the hyperactive tendon reflexes. After improvement psychological testing showed marked corresponding improvement. The electroencephalogram now showed a well sustained alpha rhythm of 10 waves per second most prominent in the occipital areas. The generalized slow waves seen in the previous tracing were greatly reduced in this record and were only recognizable in a few intermittent runs of 6 per second waves in the fronto-parietal regions. Hyperventilation produced mild emphasis of these slow waves.

Case No. 2 was admitted 1/1/56 with a history of severe nausea and vomiting, dark colored urine and failing to respond to treatment by the family physician. The impression of the referring physician was duodenal ulcer and migraine headache. The patient had been seen two months prior to admission by a neurosurgeon who made skull films and did a lumbar puncture with negative findings with the conclusion that the patient had migraine headaches. One week before admission the patient began to feel worse, developed general abdominal cramps and intractable nausea and vomiting. Two days later he passed reddish urine which looked like blood. The urine shortly became darker with brownish color, he acted peculiarly and began to stagger when he walked. He became suspicious and threatened to do violence to others. There was a brief interval during which he noted diplopia.

Physical examination on admission showed an ill-appearing man but was otherwise non-informative. Gastrointestinal series and X-ray of the chest were negative. A prior diagnosis of horseshoe kidney was verified by intravenous pyelogram. Blood count and serology were negative. The urine was pinkish amber in color and the Watson-Schwartz test for porphobilinogen was positive. All blood electrolytes were normal; NPN 27 milligrams percent. Treatment was supportive with intravenous fluids during the intractable nausea and vomiting. An electroencephalogram obtained after much improvement showed a fairly regular rhythm of 10 waves per second dominant in the occipital areas. Voltages were average to slightly above. The fronto-parietal areas showed intermittent waves in the 5 to 7 per second range seen best during hyperventilation. Slightly slow (S-1) diffuse, chiefly during hyperventilation; compatible with systemic metabolic disorder.

A search of the literature was rewarded by several cases of porphyria in which electroencephalogram findings were reported. The findings were not, however, entirely consistent. In the case of Walter[36] the EEG was reported as normal. Coffman and Kuhl[5] report that an EEG first showed tracings suggestive of an irritative high frequency activity in the right parital lead but this was considered to be within normal limits. Three weeks later a tracing revealed very fast waves and this was considered indicative of a diffuse type of cortical abnormality consistent with a toxic encephalitis. Psychologi-

cal tests on this patient showed no evidence of gross organic impairment. The patient of Kiloh and Nevin[22] had an abnormal EEG showing dominant post central rhythm of 6 per second waves and paroxysms of widespread 2 per second activity. With improvement clinically the EEG returned to normal. O'Leary[27] states that electroencephalogram in porphyria shows either a slow shift in frequency or hypersyncrony and pace irregularity may occur. He compared these changes with the statement of Adams and Foley[3] who noted that patients passing into liver coma develop paroxysmal slow sequences of 1½ to 3 per second. As the coma develops the record may become continuously that slow. Peters[29] reports one case showing 1-2 per second 100-150 microvolt waves in all leads with no localization, a basic rhythm of 3½ to 5 per second 30-140 microvolt waves with some low voltage fast activity. Another patient showed low voltage slow activity and some 5 to 6 per second 20-70 microvolt waves in all leads without localization. Duran et al.[9] made extensive studies with tracings throughout the crisis and recovery. During the acute phase they noted slow waves of high amplitude, 1 to 2 per second. After improvement the tracing returned to basically normal alpha rhythm of 8 to 9 per second but hyperventilation brought out slow waves with some spiking, mostly over the left frontal and temporal areas. Finkelman and Verde[11] report a case with EEG evidence of diffuse or diencephalic dysfunction with no evidence of an irritable focus.

Many theories as to the action of porphyrin in producing the symptom-complex of porphyria have been proposed. Denny-Brown and Sciarra[7] described lesions of ischaemic nature in peripheral nerves and cerebral white matter and cited the possibility of some locally acting vasoconstrictor substance and its relation to the visceral disorders. Rothman[33] found no changes in the nerves. Peters[28] felt from electromyographic studies of his cases that findings were consistent with postmortem findings of patchy degeneration of motor nerves. Becker[4] from his studies feels that the psychiatric and neurologic symptoms may be produced by interference with the control of the rate of hydrolysis of acetylcholine and its relation to cholinesterase by porphyrins. Watson[37] cites the possibility that the abdominal symptoms are caused by involvement of the autonomic nervous system. It is of some interest to compare the psychiatric manifestations of porphyria with those in experimental psychoses produced by lysergic acid diethylamide (LSD) and mescaline. Further, Rinaldi and Himwich,[30,31] Rinkel et al.[32] and Gestaut et al.[13] have described cerebral electrographic changes induced by LSD and mescaline. Himwich[18] gives evidence to support the probability that the effects of these drugs are the result of action on the mesodiencephalic activating system. Even though the electrographic changes are not the same (in fact, opposite), it would seem reasonable to assume that the cerebral electrographic changes in porphyria are indicative of the fact that at least a part of the action of porphyrin in producing the syndrome is central.

The treatment of a patient with an acute porphyric crisis is fraught with even more confusion. Calcium gluconate intravenously and ACTH appear to be recommended most frequently but Martin and Heck[24] do not feel that the action of these agents is fully established. They note that barbiturates and alcohol are strongly interdicted because of the propensity of these agents to induce crises, and that opiates, meperidine hydrochloride, paraldehyde and chloral hydrate do not appear to precipitate or aggravate attacks. Peters[29] has found BAL and other chelating agents effective. Lamere[23] and Freeman and Kolb[12] describe treatment with electroconvulsive therapy. Goldberg et al.[16] used ACTH, Janiff et al.[20] advocate corticotropin, Gillespie and Smith,[15] neostigmine, and Grubschmidt[17] noted remissions after procaine hydrochloride intravenously. Deperis et al.[8] describe a favorable result in treatment by means of exanguination transfusion. One may suspect that because of frequent spontaneous remissions (as in our two cases) that favorable effects may be attributed to numerous therapeutic agents and procedures. Similar conclusions have been the result in the treatment of multiple sclerosis, also notorious for spontaneous remissions. Until the nature of synthesis of the porphyrins in abnormal amounts is under-

stood, the treatment of porphyria will have to remain empirical.

Summary and Conclusions

The literature on acute intermittent porphyria is reviewed. The histories of two diagnosed cases studied, are given and cerebral electrographic abnormalities found in both these cases and those of other investigators are described. The author reasons that since the effect on the mesodiencephalic activating system of LSD and mescaline produce alterations in the EEG, those in porphyria are evidence that at least part of the production of the syndrome of porphyria is central in origin.

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Elipten in the Treatment of Organic Epilepsy

GERALD D. LAVECK, M.D.

During the pharmacological investigations of glutarimide derivatives, certain compounds were found to have definite effects on the central nervous system, specifically a sedative-hypnotic action. Some of these substances also displayed anticonvulsant properties but usually the "therapeutic index," which describes the relationship between sedative and anticonvulsant effects, was not appropriate for anticonvulsants and these compounds seemed to give no promise for better clinical effect in epilepsy than many anticonvulsants now available. However, the favorable clinical results obtained in treatment of epilepsy with the glutarimide derivative, Doriden, provided a stimulus to look for compounds of similar chemical structure which would have more specific anticonvulsant effects without adverse sedative properties. Of a great number of derivatives, it was found that Elipten, an analogue of Doriden, had a good anticonvulsant action without producing a significant sedative-hypnotic effect.[1]

Clinical studies with Elipten, a-(p-aminophenyl)-a-ethyl-glutaramide, confirmed its anticonvulsant activity, low toxicity and comparative lack of sedative-hypnotic effects.[2-4] Seizures in large numbers of patients with major, minor or mixed types of epilepsy were reported to be often completely controlled or markedly reduced in frequency, particularly when Elipten was added to an established treatment regime. Elipten also was reported to "normalize" the electroencephalogram, control status epilepticus and favorably affect the psyche.[1,2]

From Rainier School, Buckley, Washington.

The purpose of this report is to record clinical observations in mentally retarded patients with brain damage who received Elipten as an anticonvulsant in combination with other drugs.

Material and Methods

Thirty-one mentally retarded, epileptic patients with organic brain damage at Rainier School were given Elipten in an effort to better control the number and severity of seizures. All patients in the study had major motor seizures, at least one each month, and many had seizures daily; 11 had minor seizures of akinetic or myoclonic variety in addition. Neurological examinations revealed abnormal findings in 22 of the 31 patients. The majority had been tried on several anticonvulsants without achieving adequate control.

Table I shows the age distribution and type of seizures for the study population. From this it is apparent that the majority of the patients were under 15 years of age.

In September 1958, at the time the study was started, 28 of the patients were on anticonvulsants. Only three patients received Elipten as the sole medication. Therefore, in the majority of the cases, Elipten was added to other drugs which had been found in the past to be somewhat effective in controlling seizures in these patients. In general, very few changes were made in the anticonvulsant medications and new anticonvulsant drugs were not started during the study period.

Each major seizure was recorded, and the number of major seizures per month for six months prior to therapy was compared with

TABLE I

Type of Seizures and Dosage of Elipten

Age in Years	Number of Patients			
	Major Motor	Minor & Major Motor	Initial Dosage	Maximal Dosage
0 - 4	1	2	125 mg. twice daily	250 mg. twice daily
5 - 9	3	5	125 mg. twice daily	250 mg. 4 times daily
10 - 14	8	2	125 mg. 3 times daily	250 mg. 4 times daily
15 and older	8	2	125 mg. 3 times daily	250 mg. 6 times daily
	20	11		

the number of major seizures per month following therapy. No attempt was made to record the exact number of minor seizures.

Table I shows the Elipten dosage schedule employed. At weekly intervals the dose of Elipten was increased until the desired effect was obtained or until signs of toxicity developed. Eighteen patients received Elipten for at least 10 months and eight were given the medication for four to nine months. Only five patients received Elipten for less than three months. All changes in Elipten dosage were made by the author. The medical and nursing staff were aware of the study and accurate information was kept on all patients.

Response to medication was graded in the following manner. Seizures were considered to be "completely controlled" if no convulsions occurred during Elipten therapy. "Marked improvement" indicates that there was at least a 50% reduction in the number of seizures while the patient was on Elipten therapy. "Improvement" implies less than a 50% reduction of seizures. A "failure" was recorded if a patient had the same number or more seizures per month while on Elipten as compared to the six-month control period.

In addition to the clinical records just described, an electroencephalogram was obtained shortly before medication was started and a second tracing was obtained on 21 patients six to eight months after Elipten therapy was initiated. White blood cell counts, differential cell counts, hemoglobin determinations, and urinalyses were performed on two occasions during the period of observation. Cephalin flocculation and thymol turbidity tests were done on 26 of the patients after four to six months of therapy.

Results

Table II reveals the response to Elipten therapy in relation to the etiology of brain damage in the study group. Seizures were completely controlled in just one patient. Twelve patients showed a decrease in the total number of major motor seizures while 18 failed to respond in the final analysis to medication. Although no definite correlation can be made between response to Elipten and the nature of the brain lesion the data suggest that patients with postnatal infections and other postnatal disorders were more likely to respond than those with prenatal damage.

Table III shows the classification of the patients by electroencephalographic abnormalities noted prior to treatment and the response to Elipten in these categories. A much greater percentage of patients with focal electroencephalographic abnormalities failed to improve than those with a generalized dysrhythmia. The second electroencephalogram obtained four to six months after Elipten was started showed improvement in the tracing in five, no change in nine, and an increase in abnormalities in seven. No association between clinical response and

TABLE II

Etiology of Seizures and Mental Retardation and Response to Elipten

Etiology	No. of Patients	Results: Complete Control	Marked Improvement	Improvement	Failure
Congenital Cerebral Malformation	5	0	0	1	4
Cerebral Birth Injury	3	0	0	3	0
Postnatal Cerebral Infection	3	0	1	1	1
Other Postnatal Forms	4	1	1	0	2
CNS Degenerative Process	3	0	0	0	3
CNS Damage of Unknown Cause	13	0	5	0	8
Total	31	1	7	5	18

TABLE III

Electroencephalographic Abnormalities and Response to Elipten

EEG Interpretation	No. of Patients	Results: Complete Control	Marked Improvement	Improvement	Failure
Slow Dysrhythmia	12	1	4	2	5
Fast Dysrhythmia	1	0	1	0	0
Generalized Slow Spike and Wave Dysrhythmia	7	0	0	3	4
Focal Abnormalities	8	0	1	0	7
3/Second Spike and Wave Pattern	1	0	1	0	0
Hypsarhythmia	1	0	0	0	1
Borderline Abnormal	1	0	0	0	1
Total	31	1	7	5	18

improvement in the electroencephalogram was noted. Seven of the 20 individuals with major motor seizures only responded favorably to Elipten while six of the 11 patients with minor and major motor seizures showed a reduction in the frequency of major seizures. Thus the presence of minor seizures did not seem to influence the response of major seizures to Elipten. It should be emphasized that the results of therapy were based only on the number of major motor seizures recorded. In only one patient was there obvious improvement in minor motor seizures.

Frequently a marked initial improvement was noted with Elipten therapy but within one to three months an apparent tolerance developed and the seizure frequency again increased. Medication was then increased and improvement would reoccur for a short time; however, again this was not lasting. Therefore, several patients who showed marked improvement initially were finally classified as "improved" or "failure" because they were unable to maintain their improved status.

Since 28 patients in the study also received at least one additional anticonvulsant an effort was made to see if Elipten produced a synergistic effect with these other drugs. No evidence was obtained to indicate that Elipten potentiated the action of any other anticonvulsant or group of anticonvulsants.

Eleven patients had adverse responses to the drug while 20 had no side effects. Six patients became excessively drowsy, but usually this occurred when Elipten was given in a dosage greater than 250 mg. three times daily. A morbilliform rash was noted in five and generally appeared within seven to 10 days after the drug was first administered. In most of the children the rash disappeared after the dose was decreased or the drug temporarily discontinued. In one child the rash reappeared when Elipten was given for the second time and therefore the drug was discontinued. In one patient the rash occurred only after Elipten had been given for 3½ months. Also two patients became ataxic and one showed choreiform movements as side effects. Three patients showed more than one adverse effect from Elipten. It was necessary to discontinue the medication permanently in three children because of rash and in one because of drowsiness. Medication was discontinued in 12 patients after two to six months of therapy because of lack of improvement or an increase in the number of seizures. In one other patient medication was discontinued because the boy was transferred to another institution.

There was no evidence of leukopenia or other hematologic abnormalities. Two girls had albuminuria. In both of these patients the albuminuria disappeared spontaneously in two weeks and two months respectively without altering therapy. It seems unlikely that the albuminuria was related to Elipten. Liver function studies carried out on 26 patients revealed no abnormalities.

Comments

Although the results with Elipten cannot be considered spectacular, it must be remembered that the study group consisted of severely brain damaged patients who had not responded to adequate amounts of other anticonvulsant drugs. Therefore, a favorable response in 13 of 31 patients on Elipten medication indicates that this drug may be a valuable addition to the list of available anticonvulsants.

It appears that Elipten is more effective for the control of major motor seizures than for the control of akinetic or myoclonic seizures. No patients with true petit mal episodes were included in the study.

There is some indication that Elipten is more effective in controlling seizures in patients who have sustained brain damage at the time of birth or postnatally as opposed to prenatal damage or central nervous system lesions of degenerative nature. Obviously the sample is too small to statistically substantiate such an observation.

A definite tolerance to Elipten appeared to develop over a period of several weeks or months in some patients and this was a marked disadvantage.

Fabisch[4] reported that Elipten therapy was most likely to be successful in those patients who had electroencephalographic recordings with few paroxysmal signs. In our study Elipten was found to be most effective in patients who had a slow dysrhythmia

and least effective in those with focal abnormalities. Lambros[2] noted a definite improvement in "follow-up" electroencephalographic tracings in 27 patients who improved clinically while on Elipten. In the present study no association between clinical response and improvement in the electroencephalogram was noted.

The appearance of a morbilliform rash one to two weeks following the introduction of Elipten has been reported.[2-4] There is some indication that a rash from Elipten is less likely to occur if patients are started on 125 mg. of Elipten and the dose gradually increased until a therapeutic level is reached.[3]

This report indicates that Elipten may be used beneficially in combination with other anticonvulsants; therefore, it appears that Elipten may be considered a valuable adjuvant drug for the control of major seizures due to organic brain damage.

Summary

Elipten, a glutarimide derivative, appears to be a useful adjuvant drug when used in combination with other anticonvulsants in patients with epilepsy due to organic causes. A definitive favorable response occurred in 13 of 31 patients treated with Elipten. The drug was more effective in controlling major motor seizures than in minor seizures. Although toxic effects occurred in 11 individuals, medication was discontinued in only four because of these reactions. A tolerance to Elipten was observed which was a major disadvantage.

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